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Science & Innovation Management
3481646
Master Thesis

August 23 | 2014

Improving the Diagnostic System in the Netherlands

Describing the Strengths and Weaknesses of the Dutch Primary Diagnostic Innovation System

Healthcare expenditures in the Netherlands have increased almost constantly. Flaws in the Dutch primary diagnostic system can be seen as a cause of these increasing health care costs. This research is concerned with describing the strengths and weaknesses of the Dutch primary diagnostic system by comparing this system with the German primary diagnostic system. The strengths and weaknesses resulted from this research are the basis of policy recommendations, which are focused on improving the Dutch primary diagnostic system

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Preface

Diagnostics are at the heart of the healthcare process. If a patient is in need of healthcare, he or she will first visit a physician. The physician will then state a proper diagnosis, which could lead to further appropriate treatment. This shows the importance of a well-working and efficient diagnostic system to me. The diagnostic system is at the heart of healthcare system, which made it extremely interesting for me to work on this master thesis. At my internship at MSD I was provided with all the resources I needed, in order to study the Dutch primary diagnostic innovation system. By describing the strengths and the weaknesses of the Dutch primary diagnostic innovation system, I was able to formulate policy recommendation in order to improve the diagnostic system in the Netherlands and thereby healthcare in the Netherlands.

In this preface I would like to thank several persons. At first I would like to thank Prof. Dr. Ellen Moors as my internal supervisor in this master thesis. Second, I would like to thank Sjoerd Kruijff (MSD) for his commitment and support tot this research. I am also grateful for the commitment and support of Albert Zwart (U-Diagnostics). At last I would like to give my gratitude to all the interviewees for their knowledge provided and their openness.

Abbreviations

ACM	Autoriteit Consument & Mark	**LHV**	Landelijke Huisartsen Vereniging
AWBZ	Algemene Wet Bijzondere Ziektekosten	**M&I**	Modernization and Innovation
BaFin	Bundesanstalt für Finanzdienstleistungsaufsicht	**NHG**	Nederlandse Huisartsen Genootschap
BfArM	Bundesinstitut für Arzneimittel & Medizinprodukte	**NIS**	National Innovation System
BMG	Bundesministerium für Gesundheit	**NPV**	Nederlandse Patiënten Vereniging
BVA	Bundesversicherungsamt	**NVAMM**	Nederlandse Vereniging voor Arts-Assistenten Medische Microbiologie
CIBG	Centraal Informatiepunt Beroepen Gezondheidszorg	**NVKC**	Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde
CRP	C-reactive protein	**NVMM**	Nederlandse Vereniging voor Medische Microbiologie
CVZ	College voor zorgverzekeringen	**NVZ**	Nederlandse Vereniging van Ziekenhuizen
CVZ	College voor Zorgverzekeringen	**NZa**	Nederlandse Zorgautoriteit
DGKL	German United Society for Clinical Chemistry and Laboratory Medicine	**ÖGD**	Öffentlicher Gesundheitsdienst
ECRC	Experimental and Clinical Research Center	**PEI**	Paul-Ehrlich-Institute
EDC	Eerstelijns Diagnostische Centra, GP laboratory	**PKV**	Verband der Privatenkrankenversicherung
EDMA	European Diagnostic Manufacturers Association	**PoC**	Point of Care
EPD	Electronisch Patientendossier	**R&D**	Research and Development
EU	European Union	**RiLiBÄK**	Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen,
G-BA	Gemeinsamer Bundesausschus	**RIVM**	Rijksinstituut voor de Volksgezondheid en Milieuhygiëne
GKV-SV)	GKV-Spitzenverband	**RKI**	Robert-Koch-Institute
GLP	Good Laboratory Practice	**SAN**	Samenwerkende Artsenlaboratorium Nederland
GOÄ	Gebührenordnung für Ärzte	**SCP**	Sociaal en Cultureel Planbureau
GP	General Practitioner	**SEDN**	Stichting Eerstelijns Diagnostiek Nederland
IBMT	Fraunhofer Institute for Biomedical Engineering	**SHI**	statutory health insurances
IFCC	International Federation of Clinical	**SKML**	Stichting Kwaliteitsbewaking Medische

	Chemistry and Laboratory Medicin		Laboratoriumdiagnostiek
IGZ	Inspectie voor de Gezondheidszorg	**THE**	Total Healthcare Expenditures
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	**TIS**	Technological Innovation System
IT	Information Technology	**VDGH**	Verband der Diagnostica-Industrie
IVD	In-vitro Diagnostics	**ZBC**	Zelfstandige Behandelcentra
KBV	Kassenärztliche Bundesvereinigung	**ZEL**	Zorggroep Eerste Lijn
KNAW	the Koninklijke Nederlandse Akademie van Wetenshappen	**ZN**	Zorgverzekeraars Nederland
KV	Kassenärztlichen Vereinigungen	**Zvw**	Zorgverzekeringswet

Definitions

Actors	Mainly refer to organizations	**Networks**	Networks link actors (organizations) and thereby facilitate the transfer of both tacit and explicit knowledge, but also of other resources
Brokers	Part of NIS, agents who facilitate the process of knowledge and technology transfer across people, organizations and industries	**NIS approach**	The NIS approach shows the most important actors, networks institutions and their interdependencies in the primary diagnostic system
CE-mark	Guideline (98/79/EEG) for manufacturers of supporting devices and resources for the in-vitro diagnostics	**Point of Care**	PoC diagnostics refer to the diagnostic equipment (concerning mainly diabetes, CVR, CRP) that are able to conduct diagnostic tests near the patient, for instance at the GP's practice
Clinical chemistry/medical microbiology	Tests concerning clinical chemistry and medical microbiology refer to, for instance, blood sampling and bacteriological examination, and a laboratory is needed in order to analyze these tests	**Prikpost**	Prikposts are used to collect diagnostic samples
Data exchange technology	Technology focused on the exchange of data between actors in the primary diagnostic system, such as IT systems	**Primary care provider**	A primary care provider refers to a health care practitioner who consults patients that have common medical problems
Functions/key processes	Networks link actors (organizations) and thereby facilitate the transfer of both tacit and explicit knowledge, but also of other resources	**Primary diagnostic system**	In this research the primary diagnostic system refers to all the actors and institutions involved with primary diagnostics in specific country
GP laboratories	Also referred to a EDCs, laboratories used for the analyzes of primary diagnostic tests and are founded by GPs	**Primary diagnostics**	Primary diagnostics refers to diagnostics that are performed at the request of a primary care provider in the Netherlands
Hospital Laboratories	Laboratories located in hospitals used for the analyzes of primary diagnostic tests	**Private Laboratories**	In Germany the analysis of diagnostic samples can be executed at private diagnostic laboratories

in-vitro diagnostic technology	In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers	**Second line diagnostics**	Second line diagnostics refers to diagnostics executed in the context of diagnosis treatments combinations, at for instance a hospital
Institutions	Set of common habits, norms, routines, established practices, rules of laws that regulate the relations and interactions between individuals, groups, and organizations	**Self-tests**	Diagnostic tests that could be conducted by the consumers themselves
Manufacturers	Organizations focused on developing and manufacturing in-vitro diagnostic devices	**Systems of Innovation**	Systems of innovation refer to all important factors (economic, social, political, organizational, institutional and others) that influence development, diffusion and use of innovation
Motors of innovation	An acceleration as the result of feedback loops in the Technological innovation system	**TIS approach**	The TIS approach shows the dynamic strengths and weaknesses in the implementation process of the in-vitro diagnostic technology in the primary diagnostic system

Abstract

Over the past decades the healthcare expenditures in the Netherlands have increased almost constantly. Flaws in the Dutch (primary) diagnostic system can be seen as an important reason for this increase in healthcare expenditures. These flaws refer to bottlenecks resulting from the intertwinement of the primary diagnostics with diagnostic activities executed in the second line in the Netherlands. Primary diagnostics refer to diagnostics that are performed at the request of a primary care provider in the Netherlands. Second line diagnostics refer to diagnostics executed in the context of diagnosis treatments combinations, at for instance a hospital. Diagnostics have become increasingly important in lowering the increasing costs of health care, for both companies and society. As recognized by the Dutch government, improving the primary diagnostic system could be a solution to stop the trend of increasing costs of healthcare in the Netherlands. In-vitro diagnostic technology innovations could facilitate the development of the primary diagnostic innovation system. In-vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers.

In order to improve the Dutch primary diagnostic system, the strengths and weaknesses of this system have been identified in this research. By comparing the Dutch primary diagnostic innovation system with the German primary diagnostic innovation system, the strengths and weaknesses of both systems could be identified. The German primary diagnostic innovation system is perceived as more efficient (lower costs per in-vitro diagnostic test) and is therefore suitable to be compared with the Dutch primary diagnostic innovation system. Comparing both systems reveals the possible barriers in the implementation process of the in-vitro diagnostic technology in the primary diagnostic innovation system in the Netherlands and Germany. This has led to the following the research question: *What are the strengths and weaknesses of the emerging primary diagnostic innovation system in the Netherlands, focusing on the 'in-vitro diagnostic' technology, compared to Germany over the period 2009-2014?*

The the main actors and institutions, and their interdependencies, of the Dutch and German diagnostic innovation systems have been described by using the National Innovation System (NIS) approach. The dynamic Technological Innovation System (TIS) approach has been used to identify the possible barriers in the implementation process of the (emergent) in-vitro diagnostic technology in both the primary diagnostic innovation systems. Data exchange technology, such as IT systems, has also been studied in this research, due to its importance in the in-vitro diagnostic innovation system. Both the data exchange technology and the PoC technology have proven to be the emergent technologies within the in-vitro diagnostic innovation system. The TIS approach maps the seven functions/key processes over time. These system functions do not operate solely, but interact with each other. In order to analyze the system functions, a historical event analysis has been applied in this research. The better these key processes are fulfilled over time, the better the performance of the TIS is expected to be. The performance of the primary diagnostic innovation system refers to the expenditures on the primary diagnostic market in the Netherlands and Germany.

At first, the results have shown that between 2009 and 2014 one of the weaknesses of the Dutch primary diagnostic innovation system was the lack of resource mobilization. In Germany several large international companies acquired German laboratories. International companies did, however, not invest in the Dutch laboratories and the Dutch laboratories were not able to take over other laboratories. This can be seen as a barrier in the consolidation process of the Dutch laboratories, of which it is expected to reduce costs of the primary diagnostic system. Second, there is a gap between the development of knowledge in the field of the in-vitro diagnostic technology and the application of this knowledge in the Netherlands. Knowledge development (i.e. scientific studies) and knowledge diffusion (i.e. conferences and

network collaborations) in the field of in-vitro diagnostics took place in the Netherlands, but the entrepreneurial activities (i.e. new projects) were to some extent lacking behind. In Germany the amount of new projects and products was higher and many (large) organizations collaborated in order to develop new products in Germany. Third, assessment studies on the PoC technology showed many negative results. This led to negative lobbies by the Dutch government concerning the use of the PoC technology and to the lack of a sufficient reimbursement system for the PoC technology. This, on its turn, led to an absence of both niche markets and entrepreneurial activities by the large manufacturers. Fourth, the major barrier for the implementation of the data exchange technologies, such as IT-systems, is the lack of standards. Also concerns about the privacy and safety of the IT-systems have been identified, in both the Netherlands and Germany. The strengths of the Dutch primary diagnostic system refer to, at first, the role of the GP and the role of the Dutch government. In the Netherlands, the GP coordinates the health care process of the patients and thereby reduces the costs of health care. This is not the case in Germany. Second, the Dutch government (institutions) actively stimulated the primary diagnostic system by implementing new guidelines and lobbies. This has positively stimulated the consolidation process, the entrepreneurial activities, the diagnostic market and the performance of the in-vitro diagnostic innovation system.

Although the Dutch government is already involved in improving the Dutch primary diagnostic innovation system, still several improvements can be made. By stimulating the collaboration between scientists, laboratories and manufacturers, the gap between the development of knowledge and the entrepreneurial activities can be solved. Also the reimbursement system for new innovations, such as PoC devices, should be improved, so financial barriers in the implementation process of these innovations are taken away.

Table of Contents

Abstract 9

Table of Contents 11

1. Introduction 13

2. Theoretical Framework 17

2.1 Systems of innovation 17

2.2 National Systems of Innovation 17

2.3 Technological Systems of Innovation 19

2.4 Conceptualization 21

3. Methodology 23

3.1 Research Design 23

3.2 Data collection 23

3.3 Operationalization 24

3.4 Data analysis 27

3.5 Quality of the research 28

4. Results 31

4.1 The Dutch Healthcare System 31

The primary diagnostic process 31

4.2 The Dutch Primary Diagnostic Innovation System. 32

Concluding remarks 35

4.3 The Dutch In-vitro diagnostic Innovation System 36

Function 1: Entrepreneurial Activities 36

Function 2: Knowledge Development 38

Function 3: Knowledge Diffusion 43

Function 4: Guidance of the search 46

Function 5: Market formation 49

Function 6: Resource mobilization 51

Function 7: Creation of legitimacy 52

Performance 55

4.4 The German Healthcare System 56

4.5 The German Primary Diagnostic Innovation System 57

Concluding remarks 60

4.6 The German In-vitro diagnostic Innovation System 61
Function 1: Entrepreneurial activity 61
Function 2: Knowledge development 63
Function 3: Knowledge Diffusion 65
Function 4: Guidance of the search 67
Function 5: Market Formation 70
Function 6: Resource mobilization 72
Function 7: Creation of Legitimacy 75
Performance 76
5. Analysis of Results 79
5.1 Analyzing the Dutch in-vitro diagnostic innovation system 79
5.2 Analyzing the German in-vitro diagnostic innovation system 83
6. Conclusion 89
6.1 The strengths and weaknesses of the Dutch primary diagnostic innovation system 89
6.2 Policy recommendations 92
7. Discussion 95
8. References 99
9. Appendix 115
9.1 Appendix A - A country comparison: Germany 115
9.2 Appendix B – List of Interviewees 118
9.3 Appendix C – Interview schemes 119
9.4 Appendix D – Operationalization Technological Innovation System 123
9.5 Appendix E – Description of the Dutch Health care system 125
9.6 Appendix F – The Diagnostic process in the Netherlands 126
9.7 Appendix G – The Dutch primary diagnostic innovation system 127
9.8 Appendix H - 2015: A new way of funding the GP labs 138
9.9 Appendix I – The German Health care system 139
9.10 Appendix J – The German primary diagnostic innovation system 140

1. Introduction

In the Netherlands, healthcare expenditures rise every year (Rijksoverheid, 2013; de Wolf et al., 2005). This trend has cost implications for both the consumers and the government (Rijksoverheid, 2013). In order to temper this trend, changes have to be made in the healthcare system (de Wolf et al., 2005). Several studies have already been conducted concerning the reduction of costs of care in the Netherlands. Schut and van de Ven (2005), for example, have studied the effectiveness of cost-containment policies in the Dutch health care system. They show that these policies have proven to be ineffective, due to the limited role of market mechanisms (Schut and van de Ven, 2005). According to Batchelder and Miller (2006), diagnostics have become increasingly important in lowering the increasing costs of health care, for both companies and society. As acknowledged, by the Dutch government, improving the primary diagnostic system, therefore, seems to be a possible solution to this problem (Kamerbrief, 2013). Primary diagnostics refers to diagnostics that are performed at the request of a primary care provider[1] in the Netherlands (NZa, 2011a). Primary diagnostics can be divided into in-vitro diagnostics, imaging diagnostics and functional diagnostics (Kamerbrief, 2013). In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). PoC diagnostics refer to the diagnostic equipment (concerning mainly diabetes, CVR, CRP[2]) that are able to conduct diagnostic tests near the patient, for instance at the GP's practice (IHSM, 2013). PoC diagnostics are regarded as diagnostic technologies that could increase both quality and accessibility of diagnostics for the patient (Yager et al., 2008). Tests concerning clinical chemistry and medical microbiology refer to, for instance, blood sampling and bacteriological examination, and a laboratory is needed in order to analyze these tests (RIVM, 2013). Next to primary diagnostics, there is also second line diagnostics. Second line diagnostics refers to diagnostics executed in the context of diagnosis treatments combinations, at for instance a hospital (NZa, 2011b).

The importance of primary diagnostics can be derived from the fact that it influences 60- to 70% of the further medical decision-making by physicians and thereby highly influences the health care system in general (Kamerbrief, 2013). However, the current Dutch (primary) diagnostic system[3] cannot be labeled as efficient (NZa, 2011c). Different bottlenecks resulting from the intertwining of primary diagnostics with second line diagnostics can be identified in the current diagnostic system in the Netherlands (Plexus, 2010; NZa, 2011b). At first, the current Dutch diagnostic sector is characterized by a strongly fragmented supply of diagnostic activities spread over both primary and second line diagnoses (Plexus, 2010). This also leads to double funding problems and supply-driven demand. Second, bottlenecks resulting from different funding mechanisms of the different diagnostic providers can also be identified. There are several types of organizations where diagnostic measurements could be performed (Kamerbrief, 2013); for instance at a 'Primary Care Diagnostic Center (GP lab)' or at a hospital (VGZ, 2013). This leads to, inter alia, double funding of primary diagnostics and a lack of efficiency incentives (economies of scale). For example, the margins on clinical chemistry

[1] A primary care provider refers to a health care practitioner who consults people that have common medical problems (MedlinePlus, 2013)

[2] CVR refers to cardiovascular risk management and CRP refers to tests concerning infections.

[3] In this research the primary diagnostic system refers to all the actors and institutions involved with primary diagnostics in specific country

diagnostic tests could be lowered by 18% (Conqueastor, 2011). Third, bottlenecks resulting from obsolete performance and tariffs can be identified, which leads to the absence of a uniform tariff system.

Scientific research has shown that financial incentives exert a large effect on the overuse of diagnostics, and that primary diagnostics focusing on the prevention of the undesirable fragmentation of the diagnostic landscape savors great potential (Wennberg, 2004; Mulley, 2009; Song et al., 2010). Therefore, the Ministry of Health, Welfare and Sport proposed that the primary diagnostic system in the Netherlands should be strengthened in order to decrease costs of care (Kamerbrief, 2013). Developments in the in-vitro diagnostic field and primary diagnostic system could solve the double funding problem of the primary diagnostics with the second line diagnostics and lead to economies of scale (Kamerbrief, 2013; Plexus, 2010). The German primary diagnostic system is an example where the primary diagnostic system is perceived as more efficient; lower costs per (in-vitro) diagnostic test (AACB, 2013; VGZ, 2013). The primary diagnostic system in Germany is shaped in such a way that only a few large laboratories are sufficient to perform all the in-vitro diagnostic measurements in Germany (AACB, 2013). The amount of examinations per laboratory is about seven times as large when compared to the Netherlands, and the costs per examination are substantially lower (VGZ, 2013). The German primary diagnostic system is suitable to be compared with the Dutch primary diagnostic system due to the lower costs per diagnostic examination, presence of relevant technologies (Clinical chemistry, PoC etc.), quality of primary diagnostics, and similarities with the Dutch primary diagnostic system. This has been elaborated in appendix A.

Aim & Research Question

Many studies have focused on the increasing costs of healthcare and the importance of diagnostics (Bodenheimer, 2005a, 2005b, 2005c; Bodenheimer & Fernandez, 2005; Rajan & Glorikian, 2009). However there are hardly any studies focused on the entire Dutch primary diagnostic system, and improving the highly fragmented diagnostic sector (explained above). This research focuses on improving the Dutch primary diagnostic system by comparing this system with the German primary diagnostic system. This requires a more thorough understanding of both the Dutch and German (primary) diagnostic innovation system and an analysis of the technological developments in the emerging in-vitro diagnostics in both countries. Developments in the in-vitro diagnostic technology are expected to decrease the costs of the primary diagnostic system. The 'Systems of Innovation' approach can be used to identify all the key processes in the primary diagnostic innovation system and to identify all factors influencing the in-vitro diagnostic technological developments (Edquist, 2005). A National Innovation System (NIS) approach will be used to describe the most important actors, networks and institutions of the primary diagnostic system A dynamic approach (Technological Innovation System, TIS approach) has been used in order to identify the barriers in the implementation process of the (emergent) in-vitro diagnostic technology in the primary diagnostic systems over time. A comparison with the German primary diagnostic system will be very insightful since this enables to take into account system specific differences on the national level. Therefore the central question of this research is:

What are the strengths and weaknesses of the emerging primary diagnostic innovation system in the Netherlands, focusing on the 'in-vitro diagnostic' technology, compared to Germany over the period 2009-2014?

This research question will be answered by the following sub questions:

- What are the actors, networks and institutions in the Dutch primary diagnostic innovation system?
- What are the actors, networks and institutions in the German primary diagnostic innovation system?
- What are possible barriers for the development and diffusion of in-vitro diagnostics technology in the Netherlands, compared to the German primary diagnostic system over time, and why?
- How could these barriers be overcome?

Demarcation

This research focuses on identifying the strengths and weaknesses of the emerging primary diagnostic innovation system in the Netherlands. The Netherlands is chosen because of the increasing amount of critiques concerning the high costs of the healthcare sector, and the recognition of improving the primary diagnostic system as a possible solution (Kamerbrief, 2013). In order to do so, a country comparison will be made with Germany. The (emerging) technology of interest is the in-vitro diagnostics, because developments in this technology are expected to reduce the unnecessary costs being made in the current diagnostic system in the Netherlands (Rajan & Glorikjan, 2009; Kamerbrief, 2013). In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). The time period chosen for this research is from 2009 to 2014. This is based on the research conducted by Conquaestor and submitted to the Nederlandse Zorgautoriteit (NZa; a Dutch supervisory body). In this research a Dutch advisory body analyzed the cost structure of GP laboratories for 2009 (Conqueastor, 2011). The problem of inefficiency of the current Dutch primary diagnostic system and the reimbursement of diagnostic laboratory tests in specific were the motivation to this research. The research by Conqueastor (2011) can be seen as one of the first studies conducted on improving the Dutch primary diagnostic system.

Scientific relevance

This research is concerned with improving the Dutch primary diagnostic system in order to decrease the overall costs of healthcare in the Netherlands. The Dutch government has already acknowledged the possible positive effects of improving the Dutch primary diagnostic system (Kamerbrief, 2013). In a research by Hofmann (2007) it was stated that the healthcare systems worldwide would undergo huge changes. He added that technological innovation would have a large influence on these changes, and that all actors in the healthcare system will need to cooperate to bring the innovations quicker to the market. In spite of the scientific recognition of upcoming changes in the healthcare systems, not much research has been conducted towards improving the Dutch healthcare system nowadays. Several studies have focused on transformations of the Dutch healthcare system in the past. Ikkersheim and Koolman (2012), for example, studied and assessed the transformation of the Dutch hospital market in 2006. Bindels (2011) studied the transformation of the funding mechanisms in the healthcare system in the Netherlands, and Hendriks et al. (2009) studied and assessed the reform of the Dutch healthcare system when competition was allowed. Yet, scientific research has not focused on the Dutch primary diagnostic innovation system, which has led to a knowledge gap. This research makes use of the 'Systems of innovation' approach, so this research will not only contribute to scientific literature focused on healthcare and healthcare systems, but it will also contribute to scientific literature on systems of innovation approaches concerning healthcare systems.

So far, scholars in the field of technological systems of innovation approach have dedicated their efforts mainly towards the energy field (Truffer & Coenen, 2012). The health care

(pharmaceutical) sector has not gained a lot of attention yet, while this sector comprises some very specific systemic characteristics such as being highly regulated, increasing costs of product (drug) development, complex and lengthy regulatory prcedures and high technical risks (referring to low success rates for new projects and products) (Vernon & Golec, 2011).

Social relevance

This research will contribute to society by identifying possible improvements for the Dutch diagnostic sector regarding (cost) efficiency. By comparing the Dutch with the German diagnostic innovation system in which the costs of diagnostics are much lower, the Dutch diagnostic sector could improve and this could decrease the costs of diagnostics, and thus healthcare costs in general in the Netherlands. This is beneficial for both consumers and health care providers. Developments in PoC technology will increase the quality of diagnostics for the patients, since patients could then be diagnosed accurately at one point (e.g. GP) nearby. So by identifying the strengths and weaknesses of the Dutch primary diagnostic system, it becomes possible to improve the Dutch primary diagnostic system and thereby decrease the health care costs in general in the Netherlands.

Outline

Chapter 2 starts with the related theories, after which the conceptual model will be presented. The conceptual model functions as framework in this research. Chapter 3 then presents the methods and research design, and also the operationalization is stated in this chapter. In Chapter 4 the results of this research are shown. At first the NIS and TIS results for the Dutch primary diagnostic system will be illustrated, followed by the NIS and TIS results for the German diagnostic system. Chapter 5 will then show the analyzis of these results in order to come up with the conclusion of this research, which is shown in chapter 6. Finally, chapter 7 presents the discussion of this research.

2. Theoretical Framework

In this research an answer will be given to the research question: *What are the strengths and weaknesses of the emerging primary diagnostic innovation system in the Netherlands, focusing on the 'in-vitro diagnostic' technology, compared to Germany over the period 2009-2014?* In order to do so, the 'Systems of innovation' theoretical approach has been used. This chapter elaborates on the 'Systems of innovation' approach in general, followed by the explanation of the National systems of innovation (NIS) theory. At last the Technological systems of innovation (TIS) theory will be explained.

2.1 Systems of innovation

Systems of innovation refer to all important factors (economic, social, political, organizational, institutional and others) that influence development, diffusion and use of innovation (Edquist, 2005). The 'Systems of Innovation' approach is relevant for a better understanding of healthcare systems, as Marceau and Basri (2001) showed in their study of the healthcare sector of Australia. In their research, Marceau and Basri (2001) have shown that the use of innovation systems theory can be translated into political implications, even for such highly complex systems such as healthcare.

The concept of 'Systems of innovation' was introduced for the first time in published form by Freeman (1987). He defined the concept 'Systems of innovation' as "the network of institutions in the public and private sectors whose activities and interactions initiate, import, and diffuse new technologies (Freeman, 1987, p.1). In short, systems of innovation refer to all important factors (economic, social, political, organizational, institutional and others) that influence development, diffusion and use of innovation (Edquist, 2005). The main components of innovation systems are the actors (mainly organizations), networks and institutions (Edquist, 2005; Markard & Truffer, 2008). Organizations are described as "formal structures that are consciously created and have an explicit purpose. They are players or actors" (Edquist, 2005, p. 182). Institutions are described as "a set of common habits, norms, routines, established practices, rules of laws that regulate the relations and interactions between individuals, groups, and organizations. They are the rules of the game"(Edquist, 2005, p. 182). Networks link actors (organizations) and thereby facilitate the transfer of both tacit and explicit knowledge, but also of other resources (Jacobsson and Johnson, 2000). The main function of an innovation system is to pursue innovation processes, which in turn will lead to the development, diffusion and usage of innovations. In innovation systems, activities will be executed. These activities refer to the factors that influence the development, diffusion and usage of innovation (Edquist, 2005).

There are different specifications of systems of innovations. For example, systems of innovation could refer to national systems of innovation (NIS), regional systems of innovation (RIS) and technological systems of innovation (TIS) (Edquist, 2005). This research is concerned with comparing the primary diagnostic innovation system of the Netherlands with Germany. In order to do so, a NIS approach will be used. In addition, a TIS approach will be applied because it provides the opportunity to study the dynamic characteristics of emerging diagnostic innovation systems, in this case the in-vitro diagnostic technology, over time.

2.2 National Systems of Innovation

The NIS approach is relevant because markets are organized differently per NIS (Lundvall, 1992). "The behavior of agents belonging to different systems is governed by different rules and norms reflecting differences in the institutional set-up" (Lundvall, 1992, p.48). Freeman

(2002) has explained the importance of national systems of innovations by discussing the attribution of differences in rates of growth of economic regions to innovation systems. The NIS approach makes it possible to identify the relevant networks of actors and institutions in the Dutch and German primary diagnostic innovation systems (Bergek et al., 2008).

One of the criticisms on the concept of NIS is that the boundaries are not clear about what to include in the system (Lundvall, 2007). This research will therefore be structured by using the model of NIS proposed by Arnold & Kuhlmann (2001). So the boundaries in their conceptual framework have been used in this research. This conceptual framework is shown in figure 1. Arnold & Kuhlmann (2001) distinguished seven important determinants in the NIS. These determinants are (Arnold & Kuhlmann, 2001):

1. *Demand*, refers to the demand by both consumers (final demand) and producers (intermediate demand)
2. *Industrial System,* refers to large companies, small and medium sized Enterprises (SME's) and new companies. As described in the theory above, these are the actors in the innovation system.
3. *Infrastructure,* refers to the set of human and financial resources focused on innovation processes, but also the public policies focused on innovation and the mechanisms in order to protect innovation processes (i.e. IPR) (Arnold & Kuhlmann, 2001; Speirs et al., 2007)
4. *Education and Research,* refers to the presence and activity of professional education and training institutes, but also to the higher education institutes such as universities and research performed in the public sector.
5. *Political System,* refers to the intervention by the government (governance) focused on innovation.
6. *Intermediaries,* refer to research institutes or brokers. Intermediaries are bridging the Industrial system with the Education and Research. Howells (2006) states that the role of intermediaries within the innovation process can be linked to the progress of business services that are knowledge intensive.
7. *Framework conditions,* refer to those conditions such as the financial environment, taxation, propensity to innovation and entrepreneurship and mobility.

In figure 1, the model, as proposed by Arnold and Kuhlmann (2001), is illustrated. As can be seen in figure 1, the interactions between the determinants of the NIS are of importance.

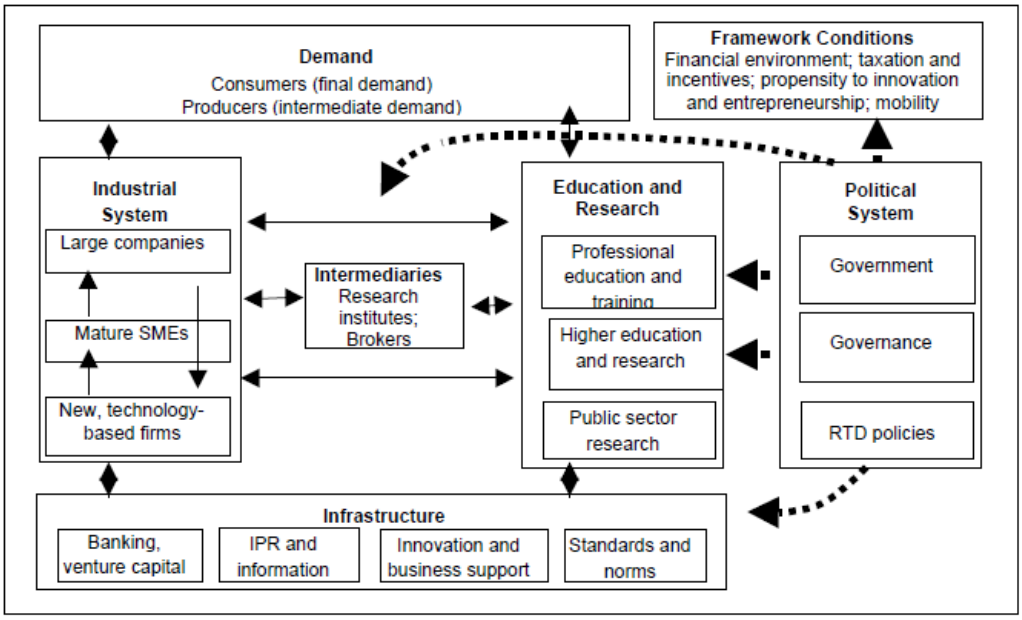

Figure 1. Model of National Innovation Systems (Arnold & Kuhlmann, 2001)

In short, the NIS approach is most suitable to describe structural characteristics of the current primary diagnostic innovation system of both the Netherlands and Germany. By using this theoretical approach an answer will be given to the sub questions 'What are the actors, networks and institutions in the Dutch primary diagnostic innovation system?' and 'What are the actors, networks and institutions in the German primary diagnostic innovation system?'

While the NIS approach mainly describes the present structure of the primary diagnostic system in the chosen countries, it hardly provides any insights in the dynamics of the emerging technologies in the primary diagnostic system over time. In order to understand the dynamics of emerging primary diagnostic system in the Netherlands, a Technological Innovation System (TIS) analysis will be performed. This TIS analysis focuses on the dynamics of the emerging in-vitro diagnostic technology since this technology makes it possible for the primary diagnostic system to become more efficient. Both the NIS and the TIS are related to each other. When looking at figure 2, it can be derived that where NIS have clear boundaries (national borders), but that the boundaries of a TIS are not defined by the nation, but by the technology (Hekkert et al., 2007).

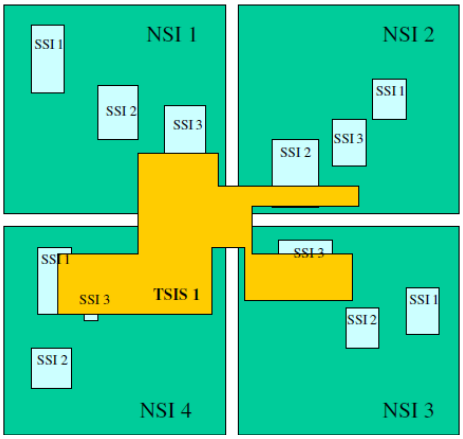

Figure 2. Different Systems of innovations (Hekkert et al., 2007)

2.3 Technological Systems of Innovation

Since this research is also concerned with technological change, i.e. the emerging in-vitro diagnostic technology[4], the Technological Innovation System (TIS) approach will be used. A TIS is a "set of networks of actors and institutions that jointly interact in a specific technological field and contribute to the generation, diffusion and utilization of variants of a new technology and/or a new product." (Markard & Truffer, 2008, p.611). According to Jacobsson and Johnson (2000), a TIS can be explained, and analyzed, in terms of its functional pattern, i.e. to which extend the functions are fulfilled over time. The functional pattern of a TIS can be mapped by analyzing the dynamics of each function separately, and by analyzing the interactions between the functions (Hekkert & Negro, 2009).

[4] In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013).

A framework has been developed by Hekkert et al. (2007) that focuses on those activities that are of importance for well performing innovation systems. These activities are labeled as functions or key processes of the innovation system. Seven functions/key processes[5] have been distinguished by Hekkert et al. (2007), namely:

1. *Entrepreneurial activities:*

Entrepreneurs are key drivers in the innovation process (Negro & Hekkert, 2008). "The role of the entrepreneur is to turn the potential of new knowledge development, networks and markets into concrete action to generate and take advantage of business opportunities." (Negro & Hekkert, 2008, p. 467). Entrepreneurs refer to both new entrants (new companies) with a vision of business opportunities and incumbent companies focused on broadening their product portfolio (larger exisiting companies) (Hekkert et al., 2007). New projects started are an example of entrepreneurial activities.

2. *Knowledge Development:*

Knowledge is important in order to develop solutions for identified problems, for example the development of a new technology (Negro & Hekkert, 2008). Possible sources of knowledge development could be through R&D, search and experimentation, but also knowledge creation through learning by using/doing and imitation. Typical examples of activities are therefore R&D projects, patents and scientific studies (Hekkert et al., 2007).

3. *Knowledge diffusion through networks:*

Next to knowledge creation, also the exchange of information (knowledge diffusion) is important. This is because information diffused through networks could lead to a change in R&D agendas (Negro & Hekkert, 2008). Knowledge diffusion makes sure that actors in the innovation systems get access to knowledge that is able to stimulate innovation.

4. *Guidance of the search:*

Resources are almost always limited, so therefore is is important that specific foci are chosen if there are several technological options (Hekkert et al., 2007). Otherwise there would be insufficient resources left for the individual options. Guidance of the search refers to those "activities within the innovation system that can positively affect the visibility and clarity of specific needs among technology users" (Negro & Hekkert, 2008, p. 468). Several determinants in the system, such as the industry or the government, could fulfill this function (Hekkert et al., 2007).

5. *Market formation:*

Since new technologies often experience difficulties when competing with existing embedded technologies, it is important to create protected spaces (markets) for new technologies (Negro & Hekkert, 2008). One of the possibilities to do so is to create niche markets (Hekkert et al., 2007). These protected spaces make it possible for actors in the innovation system to learn about the technology, and expectations can be developed. A different possibility is to create temporary competitive advantage for the new technology through favorable tax regimes (Hekkert et al., 2007).

6. *Resources mobilization:*

Basic input, resources like financial and human capital, is necessary to all the activities within the innovation system (Negro & Hekkert, 2008). The allocation of sufficient resources is necessary in order to make knowledge production possible (Hekkert et al., 2007). Examples of resource mobilization are investments in R&D, or investments made in order to allow the testing of new technologies in niche markets (Hekkert et al., 2007).

7. *Creation of legitimacy:*

[5] The functions have been labeled as 'key processes' in later research on Technological innovation systems (Wieczorek et al., 2013)

In order for a new technology to develop well, it must become part of the incumbent regime, or even overthrow the incumbent regime (Hekkert et al., 2007). Organizations that have vested interests in the current technology will often oppose to the emerging technology (Hekkert et al., 2007). Advocacy coalitions could lead to more acceptance of the new technology, which could lead to creative destruction (overthrow of the embedded technology). "If successful, advocacy coalitions will grow in size and influence; they may become powerful enough to brisk up the spirit of creative destruction" (Hekkert et al., 2007, p. 425)

Performance:

This research is concerned with the performance of the primary diagnostic innovation system in the Netherlands and Germany, by focusing on the in-vitro diagnostic technology. Performance refers to the expenditures in the primary diagnostic system, because this research is concerned with decreasing the costs of healthcare in the Netherlands.

In figure 3, a model of the TIS approach has been illustrated. As can be seen in this figure, there is no linear process notable in the TIS. The combinations of all the functions in the TIS lead to system performance, so the fulfillment of all the functions is crucial for system performance (Negro, 2007). The build-up of a TIS may undergo an acceleration as the result of feedback loops (Suurs, 2009). Functions could create feedback loops in the innovation processes and thereby stimulate innovation (Suurs, 2009). These feedback loops are labeled as motors of innovation.

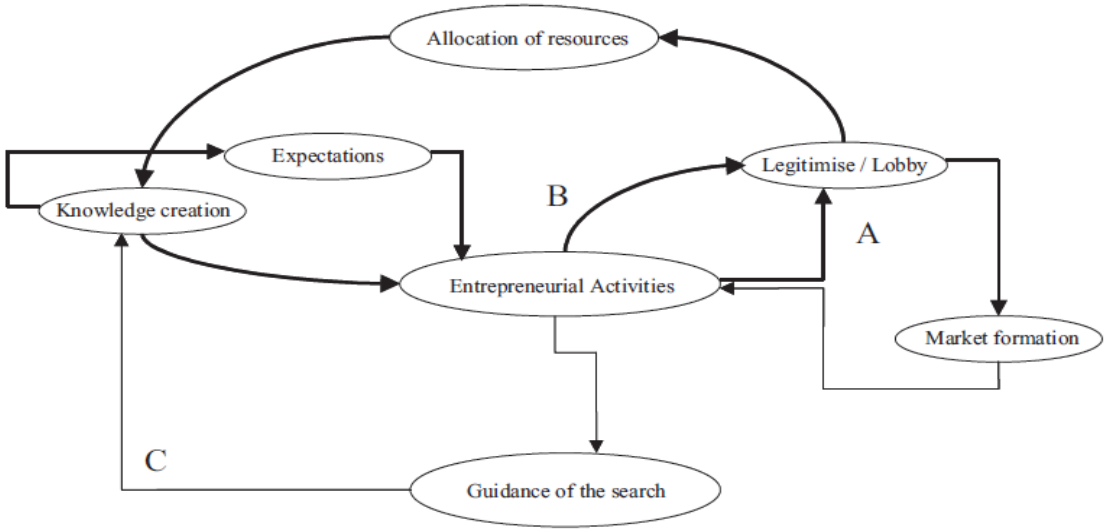

Figure 3. Technological innovation system (Negro et al., 2008)

2.4 Conceptualization

By using the NIS approach, the important actors and institutions, and their interdependencies, in the primary diagnostic system of the Netherlands and Germany have been identified. This also shows structural (dis)similarities between the current primary diagnostic system in the Netherlands and Germany. The dynamic TIS approach shows the strengths and weaknesses in the implementation process of the in-vitro diagnostic technology in the primary diagnostic system in the Netherlands and Germany in the period between 2009 and 2014. The weaknesses can be seen as barriers in this process and should be dissolved in order to optimize the process of the primary diagnostic system to become efficient.

3. Methodology

3.1 Research Design

This research is concerned with describing strengths and weaknesses of the Dutch primary diagnostic system. This will be examined by comparing the Dutch primary diagnostic system with the German primary diagnostic system, and by focusing on the emerging in-vitro diagnostic technologies within this system. This research follows a case study design, because the aim of this study is to provide an in-depth clarification of a case. "The case is an object of interest in its own right"; in this case the emergence of in-vitro diagnostics (Bryman, 2012, p.69). In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013).

This qualitative research can be divided into two parts. First a structural analysis (NIS) of the current primary diagnostic system in both countries will be carried out. Second, a dynamic analysis (TIS) will take place on the emerging in-vitro diagnostics by mapping key processes (functions) over time. (Hekkert et al. 2007). The design of this research consists of a multiple case study approach in which comparable cases are studied. The in-vitro diagnostics innovation system in the Netherlands will be compared with the in-vitro diagnostics system in Germany from a TIS point of view. In-vitro diagnostics refers to laboratory tests concerning clinical chemistry, medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). This research has also shown that data exchange technologies, for example IT systems, are of great importance in the primary diagnostic system. This technology is therefore also obtained in this research. The PoC technology and data exchange technology have proven to be emerging in the period between 2009 and 2014 (not fully implemented), while the clinical chemistry and medical microbiology technologies are already fully implemented in the primary diagnostic systems in the Netherlands and Germany.
The time period chosen for this research is from 2009 to 2014. This time period is based on the time period used in a leading report submitted to the Dutch supervisory body NZa focused on improving the Dutch primary diagnostic system by mapping the cost structure of GP laboratories.

3.2 Data collection

This research consists of several types of data collection; a scientific literature study, public sources study and interviews.

- *Public sources study*

Public sources have been used in order to collect data about statements in the society, but also studies that are not labeled as scientific are used. Health insurance companies, for instance, could have performed studies that could be useful. Financial data can also be found through public sources studies. Also newspaper articles (by using the LexisNexis database) have provided useful insights for this research. At last, grey literature has been used. A focus has been made on Dutch and English literature, and also German literature has been used. Examples of search terms that have been used are "in-vitro diagnostics", "Point-of care", "GP-laboratories" and "primary diagnostics"

- *Scientific literature study*

Scientific literature is used in order to get access to scientific knowledge about the primary diagnostic system and in-vitro diagnostics. Scopus and Google Scholar are examples of

databases of scientific literature used in this research. Scientific literature gives insights into independent statements about the relative advantage of the technology, but could also be used to identify other independent, scientific statements. The scientific literature study mainly consists of English literature. Journals such as 'Health care innovation', 'International Journal for Quality in Health Care' and 'Nature' will be of interest for the data collection. Also the leading international journal for clinical chemistry 'Clinchem' has been used. Examples of keywords are 'Primary Diagnostics', 'Point of Care', and 'in-vitro diagnostics'. Examples of search terms that have been used are "in-vitro diagnostics", "clinical chemistry", "medical microbiology" and "point of care".

- *Interviews*

In order to gather data, also interviews have been conducted with relevant actors. Eight interviews have been conducted with actors in the Dutch primary diagnostic system. Two interviews have been conducted with actors in the German primary diagnostic system. The Dutch interviewees represented different determinants of the NIS. So for example, representatives of laboratories, insurance companies and government institutions have been interviewed. The German interviewees represented a different company, not directly placed in the NIS, but possess a lot of experience and knowledge about the German primary diagnostic system. The list of interviewees is shown in appendix B. These parties were identified according to the snowball method. This means that at first interviews were held with central actors in the system, which then led to other contacts for interviews. These interviews are a source of new knowledge, but have also been used in order to verify collected data. The interviews were semi-structured, in order to capture also data of which the researcher has not thought of in the beginning. The interview schemes are shown in appendix C.

3.3 Operationalization

As already stated in the Methodology, the NIS is operationalized according to the study of Arnold and Kuhlmann (2001). The determinants and indicators are shown in table 1.

Table 1. Operationalization of the NIS approach

Conceptual Model	*Determinants*	*Indicators*
National Innovation System	Demand	Consumers (Final Demand)
		Producers (Intermediate demand)
	Industrial System	Large Companies
		Mature SMEs
		New, technology-based firms
	Infrastructure	Banking, venture capital
		IPR and information
		Innovation and business support
		Standards and norms
	Education and Research	Professional education and training
		Higher education and research
		Public sector research
	Political System	Government

		Governance
		R&D policies
	Intermediaries	Research institutes
		Brokers
	Framework Conditions	Financial environment
		Taxation and incentives
		Propensity to innovation and entrepreneurship
		Mobility

The larger part of this research is concerned with the analysis of the Dutch and German in-vitro diagnostic technology, by using the TIS approach. The functions/key processes described in the TIS approach are operationalized according to the studies executed by Suurs and Hekkert (2009) and Bergek et al. (2008). Also the study by Negro et al. (2008) has been used to operationalize the TIS approach. The functions/key processes can be measured by several indicators. These indicators can positively (+1) or negatively (-1) influence the fulfillment of the Technological Innovation System. The determinants and indicators are demarcated on life sciences instead of energy-related areas of research. In table 2 the indicators are shown, and in appendix D the indicators have been explained.

Function 1. Entrepreneurial activities
Entrepreneurial activity is needed in order for innovation to take place. The entrepreneur turns the potential of new knowledge development, markets and networks into actual action (Negro et al., 2008). The entrepreneurial activity can be measured by the amount of new projects started focused on the in-vitro diagnostic technology. It can also be measured by the amount of new products that are launched, because these products are indicators of new projects that have been started.

Function 2. Knowledge development
Knowledge has to be developed in order to provide solutions to the identified problems (Negro & Hekkert, 2008). Relevant activities are R&D projects, learning-by-doing/using, the number of patents on the in-vitro diagnostic technology, and scientific papers written on the in-vitro diagnostic technology. Investments are assigned to function 6, because investments show resource mobilization and are only the basis of knowledge development, not the result.

Function 3. Knowledge diffusion
According to Suurs & Hekkert (2009, p.1005), "the typical organizational structure of an emergent innovation system is the knowledge network, primarily facilitating information exchange". Knowledge diffusion could occur, if the actors in the system interact with each other. Knowledge diffusion could take place through conferences, workshops and annual meetings, and knowledge spillovers could occur through mergers of relevant organizations in the in-vitro diagnostic innovation system.

Function 4. Guidance of the search
Guidance of the search refers to those activities within the in-vitro diagnostic innovation system that are able to positively or negatively affect both visibility and clarity of specific needs by the users (Negro et al., 2008). Those activities refer to i.e. expectations in scientific and newspaper articles on the in-vitro diagnostic technology (negative or positive), studies on the assessment of the technology, and technological guide. Specifically in the case of the in-vitro

diagnostic technology, CE-marks are important. These CE-marks, explained in the next chapter, show that new products are approved and are able to traded without restrictions thereafter.

Function 5. Market formation
It is important to create protected spaces for new innovations, because these new innovation often encounter difficulties competing with embedded technologies (Negro et al., 2008). In order to so, niche markets for the in-vitro diagnostic technology could be created.

Function 6. Resource mobilization
"Resources in terms of both finance and human capital are necessary as basic input to all the activities within the innovation system" (Negro et al., 2008, p.468). In the case of the in-vitro diagnostic technology these resources refer to investments, in new projects and in organizations, human capital (medical specialists), and outsourcing of diagnostic activities. Since the in-vitro diagnostic technology is completely focused on the primary diagnostic system in this research, also the reimbursement of diagnostic tests is of importance.

Function 7. Creation of legitimacy
A technology has to become part of an incumbent regime, in order to develop completely (Hekkert & Negro, 2009). Another possibility is to overthrow the incumbent regime. But parties with vested interests in the incumbent regime will often act as barriers in this process. Therefore it is important to create legitimacy for the new technology. Advocacy collations often act as catalysts to create legitimacy (Hekkert & Negro, 2009). Lobbies in favor or against the in-vitro diagnostic technology are activities belonging to this function (key process). Also regulatory approval and guidelines are examples of activities that create legitimacy for the in-vitro diagnostic technology.

Performance
The performance of the TIS is measured by the expenditures on the in-vitro diagnostic market, because this research is concerned with lowering the costs of the Dutch primary diagnostic system. This is measured by the total expenditures on the in-vitro diagnostic market. Other relevant indicators are the relative expenditures on the in-vitro diagnostic market (compared to the total healthcare expenditures or per capita) and the annual growth.

Table 2. Operationalization of the TIS approach

Conceptual Model	*Determinants*	*Indicators*	*Sign/ Value*
Technological Innovation System	Entrepreneurial Activities	Portfolio expansion	+1
		Project entry/start	+1
		Project exit/failure	-1
		Product introduction	+1
	Knowledge Development	Opinion (critical notes)	-1
		Learning by exploring	+1
		Learning by doing	+1
		Research projects	+1
		Sources of knowledge	+1
		Desktop/Assessment/Feasibility studies on primary diagnostic technologies	+1
	Knowledge diffusion	Networks Coalitions	+1
		Conferences	+1
		Publishing's	+1

		Fusion	+1
	Guidance of the search	Classification, Standard setting	+1
		Doubt, uncertainty	-1
		Expectations positive	+1
		Expectations negative	-1
		Outcome study positive	+1
		Outcome study negative	-1
		Promises or targets positive	+1
		Promises or targets negative	-1
		Technological guide, Manual	+1
		CE-Mark	+1
		Approval	+1
	Market formation	Niche markets	+1
	Resource Mobilization	Investments, Subsidies	+1
		Resource refusal	-1
		Human Capital	+1
		Acquisition	+1
		Consolidation	+1
		Outsourcing	-1
		Reimbursement	+1
		Capital mobilization	+1
	Creation of legitimacy	Dissent	-1
		Lobby or advice pro	+1
		Lobby or advice contra	-1
		Regulatory approval	+1
		Advice	+1
		Guidelines	+1
Performance	*Implementation of Technology*	Expenditures on the In-vitro diagnostic market	
		Percentage of expenditures on the IVD market of total health care costs	
		Expenditures on the IVD market per capita	

3.4 Data analysis

This research makes use of an analytic induction approach. The formal objective of analytical induction is causal explanation (SAGE, 2006). It is a research strategy consisting of data collection and data analysis, which starts from the deviant case for testing models or theories developed in research. An analytic induction approach has been used because a systematic examination of similarities between multiple social phenomena will be made in order to develop ideas and/or concepts. In the first part, the Dutch primary diagnostic system is explained. Therefore all relevant actors (determinants), institutions and their interdependencies are shown. Thereafter, the same has been done for the German primary diagnostic system.

In the second part a TIS approach has been used. In this part the emerging in-vitro diagnostics technology has been examined by studying the seven functions of the TIS approach. Data has been collected in order to describe the seven functions. "System functions/key processes can be explained as (interpretative) categories of events (Suurs & Hekkert, 2009). "Within the context of a TIS analysis, an event can be defined as an instance of change with respect to actors, institutions and/or technology which is the work of one or more actors and which carries some public importance with respect to the TIS under investigation" (Suurs & Hekkert, 2009, p.1006). These events occur over time, so a historical event analysis is applied in this research. The historical event analysis is developed by Van de Ven et al. (1999) and is used in other studies by, for example, Negro et al. (2008). This approach is concerned with retrieving as many

events as possible. The events will be classified into different event categories. Every event category is allocated to one system function by using the classification scheme in table 2 (Hekkert & Negro, 2009). The contribution of an event to the realization of a system function could differ per event; some events may have a positive contribution while others contribute negatively to the diffusion of a technology (Hekkert & Negro, 2009). This is illustrated in table 4 with respectively a +1 or a -1. Eventually, this research will illustrate the positive and negative events per system function, which yields insights into the "slowing down of system growth or into controversies emerging around the analyzed technology (Hekkert & Negro, 2009, p. 587). The events are not weighted because the importance of an event is not known in advance. Eventually a storyline is presented which shows how the development of the TIS has changed over time and which also shows the role of the different system functions within this development (Hekkert & Negro, 2009). The storyline is complemented with several graphs in which the events are plotted over time. The content and chronological order of the events make it possible to identify the effect of one event or onto another, and also the order in which successful or unsuccessful (failure) events occurred. Observing reoccurring sequences of events make it possible to identify interaction patterns between system functions (Hekkert & Negro, 2009). Interviews will contribute to this history event in the sense that particular events or sequences of events can be elaborated in depth by these interviews.
The time period will be divided into two periods, from 2009 to 2011 and 2012 to 2014, based on the release by the Dutch Nederlandse Zorgautoriteit (NZa) of their official advice on the primary diagnostic system in 2011 (NZa, 2011b). After this advice, several other (governmental) institutions and organizations started showing activities towards improving the Dutch primary diagnostic system, en since then several changes have been made in the Dutch primary diagnostic system. For comparability reasons, the same division of periods has been handled for Germany.

3.5 Quality of the research

In order to preserve the quality of the research both the validity and the reliability have to be proven. According to Bryman (2008) validity can be divided into internal and external validity. Internal validity refers to whether or not there is a good match between the researchers' observations and the theoretical ideas that are developed. For each of the elements mentioned in the operationalization, indicators are presented. The indicators of the National Innovation System are based on a study performed by Arnold and Kuhlmann (2001). They have elaborated all the determinants of the NIS and therefore these indicators will be used. The indicators of the TIS are based on several highly cited studies, for instance the study on biofuels by Suurs and Hekkert (2009). Therefore the indicators represent the variables they measure which increases the validity of this research.
In order to improve the quality of the research, the data has to meet several criteria. In the case of the scientific data this means that it has to be peer reviewed if possible, and the more it has been cited the better. Other literature has to come from proper sources that are not questioned for their quality. The sources/data have to be up to date to be relevant. This means that mainly literature of the past ten years will be used. The data has also been verified by interviews with actors in both the Dutch and German primary diagnostic system. So by using the indicators, explained in the operationalization, and since the data has to be of high quality, the researchers' observations match with the theoretical ideas that are developed in this research.
External validity refers to the degree to which the findings of this research can be generalized (Bryman, 2008). Since this research only studies the Dutch primary diagnostic, focused on the in-vitro diagnostic technology, it is difficult to generalize the results of this research.

Reliability, according to Hancké (2009), is concerned with the stability of a measurement. If this study would be conducted more than once, the same results should be obtained, provided that nothing else that could be of influence has changed. The search terms used in this interview are accessible, the interview schemes are obtained in this research and the data is accessible. Also all steps of this research are presented in a clear way, so that other researchers can perform exactly the same method.

4. Results

In this chapter the results of both the NIS and TIS approaches are shown. At first the Dutch primary diagnostic innovation system (NIS) is shown, followed by the TIS analysis of the in-vitro diagnostic technology in the Netherlands. Thereafter the same approach is used for Germany. So first the German primary diagnostic innovation system (NIS) is explained, followed by the TIS analysis of the in-vitro diagnostic technology in Germany. The main technology studied in the TIS approaches is the in-vitro diagnostic technology, with a focus on the primary diagnostic systems of both countries.

4.1 The Dutch Healthcare System

The purpose of describing the primary diagnostic system in the Netherlands is to identify the relevant actors and their relationships in this system. In order to understand the primary diagnostic system, the health care system in general has been explained below and elaborated in appendix E. This system has been explained, because the primary diagnostic system is a part of the general healthcare system and therefore many actors and relationships will overlap.

The current health care system in the Netherlands can be described as a further innovation of the original "Bismarckian" social insurance system (Nivel, 2010). The Bismarckian social insurance system is founded in 1883 by a German Chancellor named Otto van Bismarck and refers to a system in which compulsory funding by both employers and employees and this is administered by pre-existing 'sickness funds' (OECD, 2011). The system has remained unchanged until 2006. The system then changed into a single compulsory insurance scheme, in which multiple health insurance companies compete for insured persons (Nivel, 2010). The main actors in the health care system in the Netherlands are the healthcare providers, health insurers and citizens (or patients/health are consumers). The role of the government has changed from a direct control of volumes, prices and productive capacity, towards the role of the setting the 'rules of the game' and monitoring whether markets are working properly (Nivel, 2010).

In order to explain the Dutch primary diagnostic innovation system, the primary diagnostic process will be explained. The description of the primary diagnostic process shows that there are various actors operating in the primary diagnostic innovation system. This process has been further explained in appendix F.

The primary diagnostic process

As explained in the introduction, primary diagnostics refers to diagnostic services that are performed at the request of a primary care provider[6] in the Netherlands (NZa, 2011a). The basis of the diagnosis is the anamnesis (Eekhof, 2012). The anamnesis refers to the visual identification of symptioms of diseases by GPs, everything spontaneous told by the patient and specific questions by the GP asked to the patient (Eekhof, 2012). If further diagnostic research is needed, the primary care provider, such as the GP, could make a request for the application to perform diagnostic tests. The next step refers to the execution of the in-vitro diagnostic examination. Within the execution of primary diagnostic tests, two sub steps can be distinguished; namely the collection of the patient's material (diagnostic sample) and the analysis of the patient's material. The last step refers to the interpretation of the diagnostic

[6] A primary care provider refers to a health care practitioner who consults patients that have common medical problems (MedlinePlus, 2013)

tests and advice to the GP. The evaluation of the tests eventually leads to a diagnosis, or at least the exclusion of a condition.

4.2 The Dutch Primary Diagnostic Innovation System.

This chapter gives an answer to the sub question 'What are the actors, networks and institutions in the Dutch primary diagnostic innovation system?' In figure 4, the conceptual framework as given by Arnold and Kuhlmann (2001), has been used in order to illustrate the Dutch primary diagnostic innovation system. This section will briefly explain this figure. This has been elaborated in appendix G.

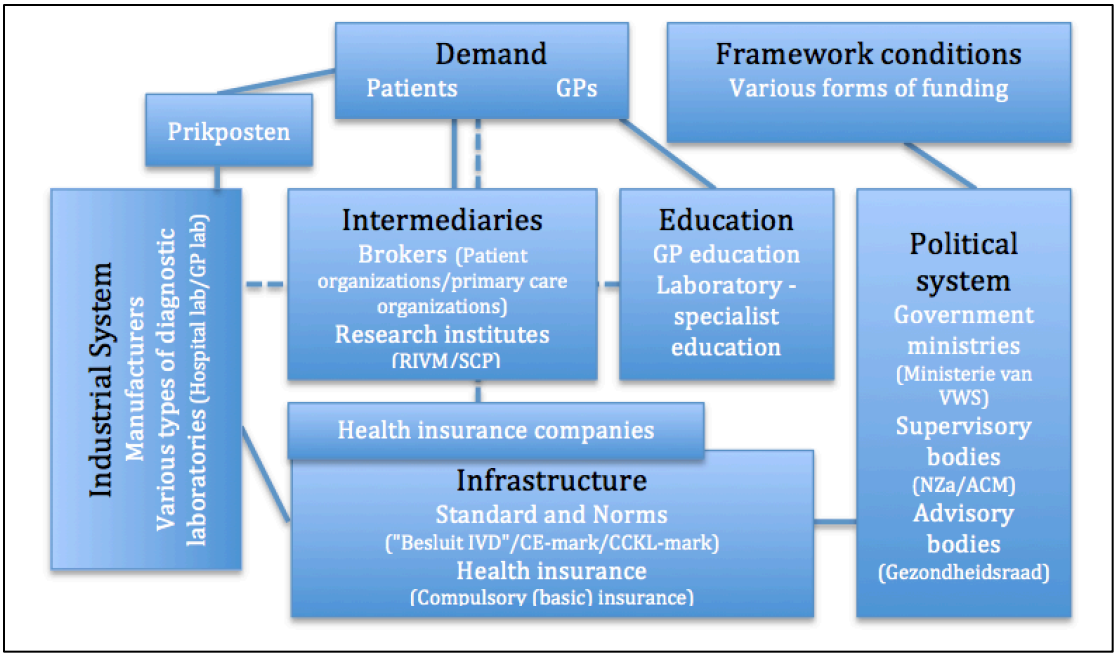

Figure 4. The Dutch primary diagnostic innovation system

The first component is **Demand**. Demand refers to both the final demand, as well as intermediate demand of primary diagnosis (Arnold & Kuhlmann, 2006). In the case of the Dutch primary diagnostic innovation system the final demand refers to the patient or the healthcare consumer and the intermediate demand refers to the primary care provider, for instance the general practitioner (Diagned, 2012; NZa, 2011a). This is acknowledged by respondent A. As explained above, *the patient (primary care consumer)* seeks for health advice at the primary care provider (NZa, 2011a; Vektis, 2013). *Primary care providers* refer to GP's, but also to pharmacists, physiotherapists, obstetricians, remedial therapists, dietitians, speech therapists, nurses and care providers in home care, general social workers and primary psychologists (Nivel, 2011). Since this research is concerned with in-vitro diagnostics, the focus of the primary diagnostic innovation system will be mainly on the GP. This is because GPs in the Netherlands have a gatekeeping role (Linden et al., 2003; Vektis, 2013). Citizens with health complaints first go the GP, after which they could receive a referral to specialist care (for instance at the hospital) if needed (LHV, 2011). The GP determines the diagnosis and the associated care (LHV, 2011).

The **Industrial system** can be divided into two parts. The first part includes the developers/manufacturers of in-vitro diagnostic devices. The second part refers to the organizations involved in the actual collection and analysis of patient tissue/blood samples the

in-vitro diagnostic process. In the Netherlands there are several organizations specialized in the development and *manufacturing of in-vitro diagnostic devices* (Diagned, 2014a). There is a Dutch umbrella organization for manufacturers and importers of in-vitro diagnostic devices, called Diagned (Diagned, 2014a). Diagned represents over 30 manufacturers and importers of in-vitro diagnostic devices, both large and smaller companies. The large manufacturers in the Netherlands are Abbott Laboratories (Diagnostic Care), Roche (Diagnostics), BioMérieux, Beckman Coulter, Beckton Dickinson Company, Sysmex, Siemens and Ortho Clinical Diagnostics. Other large in-vitro diagnostics manufacturers in the Netherlands are for example the Dutch company Philips Healthcare (Diagned, 2014b). Respondent A stated that the influence of in-vitro diagnostic manufacturers on the primary diagnostic system is both small and large. It is small in the sense that these manufacturers do hardly influence the decision-making processes by the NZa and government. But influence is large in the sense that manufacturers are seen as strategic partners of their customers (laboratories) and think ahead for solutions to (upcoming) problems in the market. Technological development (innovation) by the manufacturers is the result of acquisitions of (small) companies, collaborations and acquisitions of patents of technology transfer offices, but also of trend watching in the market. Also experts in the market are consulted for their knowledge on technological developments. Respondent A labeled this as mutual cross-fertilization. The same interview showed that manufacturers keep in touch with almost all organizations that are engaged in in-vitro diagnostic activities, such as GPs, healthcare groups, hospitals, laboratory specialists, GP laboratories, and healthcare insurance companies. The second part of the 'Industrial system' refers to the organizations involved in the *collection and analysis in the in-vitro diagnostic process*. The difference with the primary care providers in the 'Demand' determinant is the focus of these organizations on purely the execution and analysis of in-vitro diagnostics for the patients of the primary care providers (NZa, 2011a). There are different kinds of organizations able to collect and analyze the diagnostic samples. The most relevant organizations are (NZa, 2011a):

- GP labs. GP labs are also referred to as primary diagnostic centers (Eerstelijns Diagnostische Centra, EDC's). At GP labs laboratory research, imaging diagnostics (for instance echo and MRI) and function diagnostics (ECG, pulmonary function) are being performed, at the request of the primary care provider. The GP labs make use of 'prikposten[7]' in order to collect patient material (diagnostic samples), for instance blood. Several GP labs, however, made it possible for the patient to have their patient material collected at home (Atal-MDC, 2014; DCWF, 2014; Certe, 2014a). Interviews have shown that almost all GP labs are foundations. Respondent B showed that to make use of the tariff lists by the NZa (explained below), a GP lab has to be (part of) a foundation. GP laboratories are not focused on generating profit (De Wildt & Janssen; 2006).
- Hospitals. Hospitals posses their own laboratories, features for imaging diagnostics and function diagnostics. A large share of the hospitals provides both second line diagnostics, as well as primary diagnostics. Hospitals also offer services concerning the collection of patient material, just like the GP labs mentioned above (UMCU, 2014).

In the Netherlands there are around 60 to 70 hospital laboratories active in the primary diagnostic innovation system, and there are circa 23 EDC's located in the Netherlands. These laboratories and EDC's differ in their size and catchment areas (NZa, 2011a). The other types of organization are explained in appendix G.

[7] A "prikpost" is a place where diagnostic samples, such as blood samples, can be taken from the patient. A "prik post" could be located near hospitals or GPs, but also in different places.

The **Political system** can be divided into three components in the Netherlands; the government ministries, the supervisory bodies and the advisory bodies. When looking at the Dutch health care system, several *government ministries* possess some influence. The Ministry of Health, Welfare and Sport, a separate administrative body, develops policies in order to ensure the well-being and health of the population in the Netherlands (Ministerie van VWS, 2014). The second relevant government ministry is the Ministry of Social Affairs and Employment, because they possess responsibilities for health-related social security schemes covering sickness benefits and disability benefits outside of the health insurance scheme (Ministerie van SZW; 2014; Nivel, 2010). However, the provision of health care services is largely based on private initiatives, which leads to a limited role of the Dutch government in the delivery of health care services (Nivel, 2010). One of the *supervisory bodies* in the Dutch primary diagnostic innovation system is the Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZa). The NZa is an independent administrative body in the Netherlands (NZa, 2014a). The NZa is responsible for supervising the three health care markets in the Netherlands; namely the health provision market, health insurance market and the health purchasing market (Nivel, 2010). The NZa is thereby authorized to (1) impose tariff- and performance regulation, (2) it may request adapting price setting in line with NZa rules of those players that have obtained significant market power and have raised their prices too highly, and (3) has authority to set up general rules for healthcare providers and health insurers to increase the transparency of the market for consumers (NZa, 2014a). Another example of a Dutch supervisory body is the Health Care Inspectorate (Inspectie voor de Gezondheidszorg, IGZ), which is an independent organization that supervises the accessibility and quality of health care in the Netherlands (IGZ, 2014a). The Dutch competition regulator (Autoriteit Consument & Mark, ACM) has the general task to enforce fair competition in all sectors of the Dutch economy, for instance in the health care sector (Nivel, 2010; ACM, 2014a). An important *advisory body* is the Health Council (Gezondheidsraad), which gives advice to the Ministry of Health, Welfare and Sport on the scientific state of the art in health care, public health, medicine and environmental protection (Gezondheidsraad, 2014).

The **Intermediaries** can be divided into brokers and research institutes (Arnold & Kuhlmann, 2001). *Brokers* are described as agents who facilitate the process of knowledge and technology transfer across people, organizations and industries (Howells, 2006). Important brokers in the Dutch primary diagnostic innovation system are the patient organizations and umbrella organizations for primary health care providers and GP laboratories. Patient organizations are focused on representing the interests of the affiliated health care consumers (Artsennet, 2014; NPCF, 2014). One of the largest *research institutes* is the National Institute for Public health and the Environment (Rijksinstituut voor de Volksgezondheid en Milieuhygiëne, RIVM) (Nivel, 2010). Other examples of brokers and research institutes are explained in appendix G.

The **Educational system** shows that there are several educational organizations in the Netherlands focused on primary diagnostics. Education programs are available to students to become GPs, laboratory specialists, and medical laboratory research (Anno73, 2014; VUMC, 2014; NVKC, 2014a).

Infrastructure refers to the standards & norms, and health insurances, because the health care market is highly regulated, and health insurances play a significant role (Field, 2008). As explained by Diagned (2012), the *quality of the in-vitro diagnostics (Standards and norms)* rests on two cornerstones; namely safe and effective diagnostic tests on the one hand and professional use on the other hand. The quality demands for both the product (devices) as well as the usage of these products are recorded in laws and regulations; “Besluit IVD”, “Besluit medische hulpmiddelen” and “Kwaliteitswet zorginstellingen” (Diagned, 2012; Overheid, 2014a; Overheid, 2014b). The industry (manufacturers) and laboratories are all responsible for

proper and safe usage of in-vitro diagnostics. The IGZ supervises the compliance of the relevant actors to the laws and regulations (Diagned, 2012). Other important regulations are the CE-mark and the CCKL-mark (NVKC, 2014b; RVO, 2014). The CE marking is a guideline (98/79/EEG) for manufacturers of supporting devices and resources for the in-vitro diagnostics and the products that are subject to this guideline have to meet several essential criteria (RVO, 2014). The CCKL-mark is a quality mark shows that the laboratory handles the offered patient materials carefully and discreet (Elkerliek, 2014). The *health insurance* consists of the basic health insurance, which is obligatory to have, and the supplementary insurance (Rijksoverheid, 2014a). Every citizen in the Netherlands is obliged to have a health insurance (Rijksoverheid, 2014a). The main tasks of the health insurance companies, as explained by respondent C, are to acquire enough health care for their clients, but also to influence the costs, quality and customer experience of the health care system. Respondent C saw it as a main task of the health insurance company to provide the health care market, and the diagnostic market, with incentives to operate more efficiently.

Framework conditions refer to the financial environment, taxation and incentives, propensity to innovation and entrepreneurs and mobility (Arnold & Kuhlmann, 2001). Important in the financial environment is the *funding and reimbursement* of the relevant actors, since this is one of the problems of the Dutch primary diagnostic system described by the NZa (2011) of the Dutch primary diagnostic system (NZa, 2011). The primary diagnostic activities executed by the GP are mainly reimbursed according to the Modernization and Innovation (M&I) module (Vektis, 2013). This module makes it possible to charge several services such as diagnostics like ultrasound examination for which free pricing is applied (NZa, 2011). The tariffs claimed by the EDC's are obtained in a list called the "Tarievenlijst Eerstelijnsdiagnostiek", established by the NZa (NZa, 2013a). As of 2014, the funding of the GP laboratories changed from budget funding into performance funding, as will be explained in the textbox "2015: A new way of funding the GP labs" (NZa, 2013b). Hospitals are performance funded since the year 2012; until then hospitals were also budget funded (Kamerbrief, 2013). The type of funding of the other types of primary diagnostic organizations has been explained in appendix G.

Concluding remarks

This chapter has given an answer to the sub question *What are the determinants and interdependencies of the Dutch primary diagnostic system?* The Dutch primary diagnostic innovation system has shown that 'Demand' includes the patients and GPs, while the 'Industrial system' can be divided into manufacturers of in-vitro diagnostic devices and the various types of laboratories. The GP laboratories make use of 'prikposten'. The patients get their diagnostic samples collected at these 'prikposten', which are then sent to the laboratories to be analyzed. The 'Political system' determinant has shown that both government ministries, as well as supervisory and advisory bodies influence the whole primary diagnostic system. Health insurance companies are highlighted in this scheme because they hold and divide the healthcare budgets. These insurance companies therefore highly influence especially the laboratories, GPs and patients.

2015: A new way of funding the GP labs

The GP labs were budget funded until the first of January 2014. In 2014, the NZa implemented the policy guideline 'Eerstelijnsdiagnostiek' (TB/CU-7041-03). In this policy, it has been determined that maximum tariffs will be used for the suppliers and that the transition will be made from budget funding to performance funding for GP labs (NZa, 2013b). The year 2014 will be used as a year of transition (NZa, 2013b). This transition model enables the GP labs to adjust their business operations and management to the performance-funding model, and to generate 15% equity (NZa, 2013b). The transition model will also minimize any budgetary consequences during the transition period (NZa, 2013b; SAN, 2013). The GP labs are allowed to grow with 2.5% every year (Daris, 2013). The maximum tariffs have also been recalibrated on the basis of a new investigation regarding the costs of the diagnostic services. This has not been done since 2003, however the tariffs have been indexed yearly (NZa, 2013b). Due to technological developments, costs of the diagnostic services have dropped over the years but the tariffs have not been changed according to these drops (NZa, 2013b). In other words, prices were too high, and the market was old and archaic.

The reason for this policy guideline is the persistent criticisms on the funding of the GP labs (Engelenburg, 2013). In the situation of budget funding, the GP labs had no incentives to operate more efficient, because they worked with fixed tariffs and a budget (Engelenburg, 2013). Hospitals, on the other hand, had discovered in-vitro diagnostics as an extra source of revenues a few years ago to fund expensive other 2nd line services (Olsthoorn, 2011). But this has led to a situation of separated files by the different health care providers, and unusable and badly exchangeable data between them (Financieel Dagblad, 2011). Therefore primary diagnostic experts have mentioned the importance of infrastructure for the laboratory diagnostics (Financieel Dagblad, 2011). An example could be a situation in which the hospital would perform all the diagnostic analyzes for the GPs, which would lead to cost effective and high quality analyzes (Financieel Dagblad, 2011). Other possibilities in order to reduce the costs of diagnostics are mergers between GP labs and/or hospitals (Engelenburg, 2011). Already some hospitals have merged, as well as several GP labs. Mergers make it possible for GP labs to obtain economies of scale, thereby work more efficient and decrease the costs of their diagnostic services (Engelenburg, 2011). Volume is important in this sector, because 85% of the operations performed in GP labs are routine based. So the higher the volume, the lower the cost per test (Engelenburg, 2011). Health insurers will now be able to choose between the most efficient GP labs or hospitals, which will be another incentive to operate more efficient (Engelenburg, 2011). Respondent C showed that healthcare insurance companies also control the volume of the diagnostic tests because one of the main tasks of the company is the procurement of healthcare. So the health insurance companies in the Netherlands control both the volumes and costs of the diagnostic market. This is further explained in appendix H

4.3 The Dutch In-vitro diagnostic Innovation System

In this chapter, the Dutch in-vitro diagnostic technological innovation system will be explained. The in-vitro diagnostic technology refers to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). Since this research is concerned with improving the primary diagnostic system, the results described below are focused on the primary diagnostic system. All seven functions/key processes of the TIS approach are explained below. The time period will be divided into two periods, from 2009 to 2011 and 2012 to 2014, based on the release by the Dutch NZa of their official advice on the primary diagnostic system in 2011 (NZa, 2011b).

Function 1: Entrepreneurial Activities

The results of the Entrepreneurial activities in the Netherlands are shown in figure 5.

2009-2011

In 2009, several technologies were introduced concerning the exchange of information between the patient and GP, GP and GP laboratory or between other actors such as the GP laboratory and a hospital laboratory. The Electronic Health Record (Electronisch Patientendossier, EPD) is an example of such a technology. The EPD is seen as an entrepreneurial activity because it is a project focused on making it possible for healthcare providers to exchange information about patients and their medical status (Rijksoverheid, 2014b). In 2009, for example, the Spaarne Ziekenhuis started with an EPD-like project. This project should have made it possible for the hospital to gather all the medical information at one central digital place and thereby support the complete process of the patient form beginning to end. One article reports the evaluation of several projects focused on the information exchange problem. One of these projects focused on

digitalizing the request by the GP for a specific test. Until then these requests were filed by hand. One other project focused on automatic responses to the healthcare provider, who requests the test. This response contained the results of the tests. In 2010 a plan for a project was introduced, which can be seen as an alternative to the EPD. A senior manager at Arteria consulting proposed this project. It was called the "Kerndossier" and was merely a professional summary of the most important patient data. A chip on a health insurance card could contain al this information. Nothing was stated about the execution of this project. In 2011, a project started concerning information exchange between GPs and several hospitals in the Netherlands. But also in 2011 it was published that the EPD, and all its projects, were cancelled because the consumers of the EPD (GPs, pharmacists and hospitals) were not interested enough. This was stated by the one of the first project leaders of the EPD. The main concerns related to privacy infringement and safety issues.

In the period between 2009-2011 also several projects started in the field of clinical chemistry and PoC technologies. In 2009 a project was started by the Medisch Centrum Alkmaar, which aimed to develop a PoC device. In this year Ostendum, a spin-off of the university of Twente, also developed a new diagnostic device. In 2010 and 2011 it was reported that several projects were started, focused on new ways of analyzing data and thereby providing the diagnosis in the Netherlands. In 2011, Biocartis and Janssen Pharmaceuticals started a project in order to develop a device that is able to provide a quick and accurate diagnosis for patients, based on biological molecules (biomarkers) in human material. In the same year Biocartis introduced a new product that is able to detect diseases such as Alzheimer's diseases and various types of cancer. It was also in 2011 that the "e-nose", a diagnostic device, was introduced by the university hospital AMC. This diagnostic device is reliable for 90% and is designed to detect asthma and COPD.

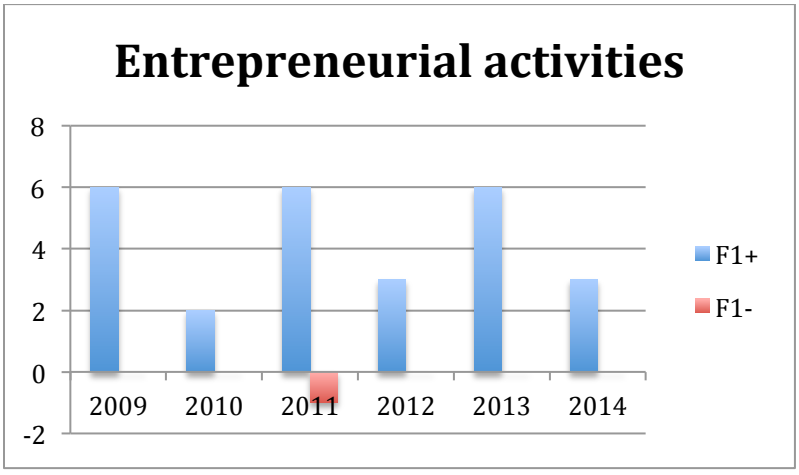

Figure 5. Function 1. Entrepreneurial activities in the Netherlands

2012-2014

In 2012 a project by the Jeroen Bosch Ziekenhuis started focused on transferring PoC activities to the GP practice. Several devices were installed at the GP's office and the assistants of the GP were instructed in the usage of the PoC devices. Also activities concerning the information exchange have been identified in this period. One newspaper article reported about a new agreement on the EPD, in which health insurers, healthcare providers and patients agreed on the terms. In 2013, two hospitals, the UMC Utrecht and St. Antonius Ziekenhuis, concluded an alliance and with this alliance the EPDs were combined. In the same year, a center (SHO centra)

for medical diagnosis started a pilot focused on facilitating the health care provider with the possibility to request their tests digital without any paper works. Also a project started with the goal to reduce the amount of double diagnostic procedures, by improving the information exchange between the actors in the primary diagnostic system. This project was started by a GP laboratory (Diagnostiek voor U), and involved the use of data exchange technology. By using this technology, the specialist at the hospital had the opportunity to make use of the results of prior diagnostic tests. In 2013 a contest started to develop new medical devices. The result of the contest was the development of a "Tricorder" (as in the Star Trek movies) that could monitor the pulse rate, blood pressure, breathing, temperature and oxygen level of patients. The data could then be linked to common diseases. Also projects started concerning the logistics of the gathered blood samples of patients in this period. One project focused particularly on improving the logistics, where a different project in 2014 focused on using just one courier for all the participating GPs. This courier collects all the diagnostic samples at the GPs, and then delivers these samples to the laboratories where the analysis takes place.

Both respondent C and D stated that technological developments in the in-vitro diagnostics are important because it could lead to lower costs per test and to an increase in supply. The health insurance company cannot exert any influence on this, but keeps track of the technological processes and let them become informed by experts in the field. But an increase in supply will lead to an increase in demand, which could lead to a huge increase in the volume of diagnostic tests performed and analyzed. This could increase the overall costs of the primary diagnostic system.

The function "Entrepreneurial activities" has shown that projects have been started and products have been introduced for the clinical chemistry technology, PoC technology and information exchange technology over all the years. The failure of the EPD project, however, can be seen as project that has been cancelled.

Function 2: Knowledge Development

The results of the Knowledge development in the Netherlands are shown in figure 6

2009-2011

In the period between 2009 and 2011 several R&D projects started concerning the clinical chemistry technology and also activities concerning "learning by doing" have been identified. These latter activities refer to an improved interpretation of tests, which increased the reliability of the test results, and to the increased ability of GPs to directly request and evaluate tests such as blood, urine, X-ray and MRI-tests. A director of Meditta, an umbrella organization for GP practices, stated this in 2011. The University of Twente educates technical physicians that are able to support the diagnostic process in a better way, and conducts research in the field of in-vitro diagnostics at the Mira-institute.

This period also shows that there were several negative opinions on the quality and usage of PoC devices. PoC devices for diagnosing diabetes were perceived as unreliable. A researcher in the Netherlands therefore concluded that the PoC devices are not suitable for that specific diagnosis. In 2010, concerns were raised about the bad presentation to GPs and other physicians of all the data that should lead to a diagnosis. This bad presentation led to diagnostic problems and even diagnostic mistakes. This is also acknowledged by an author who wrote that GPs get their information about patients fragmentary and this is not beneficial to the quality of the diagnosis. Respondent E has also stated that there are too many IT systems that are not able to communicate with each other.

In 2011, Erna Lenters (PHD in Medical Sciences) expressed critiques on the usage of PoC devices for diabetes. She explained that these problems refer to both the accuracy of the devices, but also the usage by both the GPs (or assistants) and the patients. These problems made Lenters to raise her concerns about these devices and even to warn the society for the usage and test results of these devices.
In the field of medical microbiology there was a research in 2009 focused on Molecular detection of intestinal parasites for clinical diagnosis and epidemiology. But also research has been conducted on the identification of biomarkers for the diagnosis of depression, as well as an R&D project by a collaboration between Future Diagnostics and Philips on a small device for blood testing.

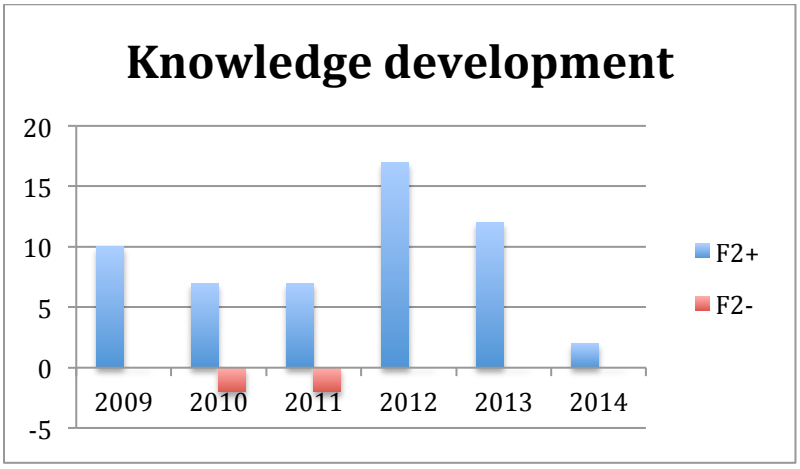

Figure 6. Function 2. Knowledge development in the Netherlands

2012-2014
The period between 2012 and 2014 showed that many R&D projects were focused on the clinical chemistry technology, or at least the medical laboratory technology. Interesting is the development of so called "lab-on-a-chip" technologies, which make it possible to analyze a proper diagnosis with only a chip. Patients themselves could therefore use these technologies at home. Researchers at the University of Twente, for example, have developed such a chip in 2012. This device made it possible to provide the applicant with a decisive answer about a possible infection with bacteria or viruses within three minutes. Also other chips have been developed, namely a chip for fertility, and a chip to measure the lithium level in human blood samples. In 2012, research has been conducted on identifying bacteria in urine, which could then be used for several diagnostic procedures. This R&D project also included the development of a new product. This research has been conducted in Leeuwarden, the Netherlands. In 2014, a research started to identify several types of cancer through blood tests. This research is being conducted by an international group of scientists, in collaboration with the Antoni van Leeuwenhoek institute in Amsterdam.
When looking at the PoC technology, one opinion, by a researcher of the Saltro (GP laboratory), has been identified in the period between 2012-2014. He believes that it should be used more often; patients should have the ability to make use of this technology since the efficacy is already proved scientifically.

In the field of medical microbiology many R&D projects have been conducted in 2012 and 2013. In 2012, for example, scientific research started towards the detection of several antibodies that could be used for the clinically identification of Borrelia infection. In 2013, scientific

research started towards the improvement of the diagnosis of Chlamydia trachomatis, as well as for Lyme disease.

Respondent A showed that research in the Netherlands is excellent, but he also showed that turning research into turnkey applications is lacking. In the Netherlands there also is a high coverage ration of both hospitals and GP laboratories. So there are developments focused on improving the efficiency and turnaround times of devices, but there is a lack of focus on achieving volume efficiencies (economies of scale).

Patent analysis

The patent analysis shows the volume and the type of patents that have been applied for in the period between 2009 and 2014. This is shown in figure 7. This gives insights in the knowledge development through patent applications for the in-vitro diagnostic technology. The data are the same for the Netherlands and Germany, because the patent analysis shows international results.

2009-2011

The search terms used for the patent analysis refer to the technology that is studied in this research: in-vitro diagnosis. The other search terms are the elements of this technology, namely clinical chemistry, Point of Care, medical microbiology and Self-tests. The results are shown in figure 7. In the first period (2009-2011), 158 patents have been applied for in the field of in-vitro diagnostics. As for the whole period (2009-2014), the search term 'in-vitro diagnosis' showed the highest number of patent applications (219) and 112 in the period 2009-2011. Using the other search terms led to less patent applications in this period.

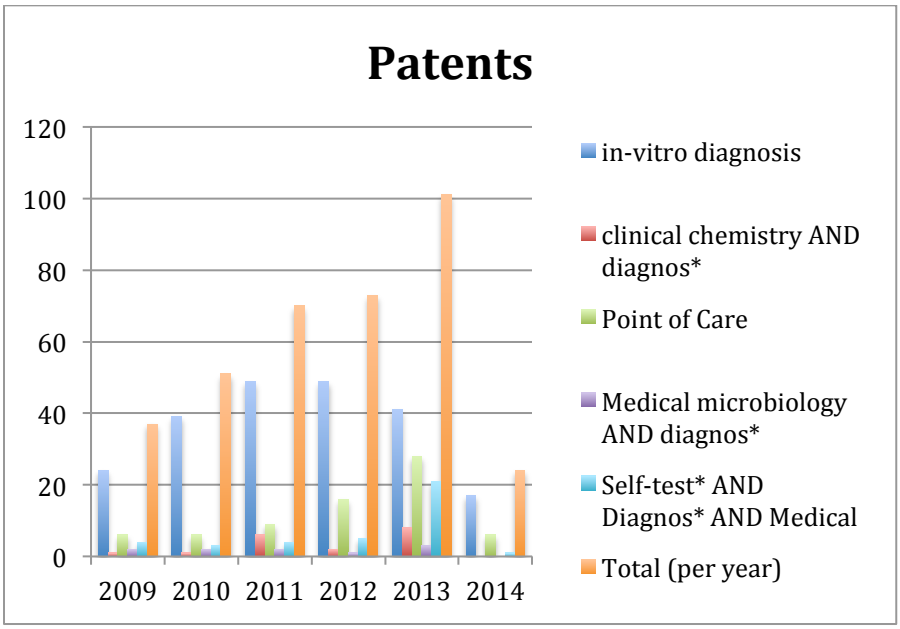

Figure 7. Patent analysis (worldwide)

2012-2014

When looking at the two periods (2009-2011 and 2012-2014), it can be stated that within the second period more patents have been applied for. These results show that there is an increase

of patent applications in the period from 2009 to 2013 (2014 not included since it has not ended yet), and in 2013 there was a higher increase of patent applications than the years before. The reason for this is that in 2013 a higher number of Point of Care and Self-test patents have been applied for. Also in 2012 the number of patent applications for Point of Care showed a large increase with respect to the previous year.

In both periods many of the patents of the search term 'in-vitro diagnosis' refer to labeling of certain compounds, new biomarkers, or methods and compositions for diagnosing diseases. An example is "An in vitro method for diagnosing of endometriosis" in 2013 (WO2013171655 (A1)), applied for by Signorile Pietro Giulio (Italy). The search terms 'clinical chemistry' and 'medical microbiology' showed results referring to compounds, methods for preparing substances for diagnosis and other resources used for diagnostic related activities. The search terms 'Point of Care' and 'Self-test' show results for new (components of) devices, methods, and other resources used for diagnostic related activities.

It can be concluded that over the years more patents have been applied for. Patents in the field of Point of care have increased every year, which shows that this is becoming more and more a focus of new research and possibly development. This is to some extend also the case for the clinical chemistry and medical microbiology technologies, although there was a dip of patent applications in 2012 for both.

Scientific Article analysis

The scientific article analysis shows the volume and the focus of scientific articles that have been published for in the period between 2009 and 2014. This is shown in figure 8. This gives insights in the knowledge development through patent applications. The data are the same for the Netherlands and Germany, because the Scientific article analysis shows international results

2009-2011

Also the search terms used for the scientific articles analysis refer to the technology that is studied in this research: in-vitro diagnosis. The other search terms are the elements of this technology, namely clinical chemistry, Point of Care, medical microbiology and Self-tests. The results are shown in figure 8. This period shows 384 results (715 results in total). The search term 'Point of Care' shows the most results (156 results over the period 2009-2011) followed by 'clinical chemistry' (109 results over the same period). In contrast to the patent analysis, using the search term 'in-vitro diagnosis' gave almost the lowest number of results (52 results in the period 2009-2011 and 85 results in the period 2009-2014). The reason for this could be that the search term is not specific enough for scientific research, as it can be divided into sub-technologies as described above.

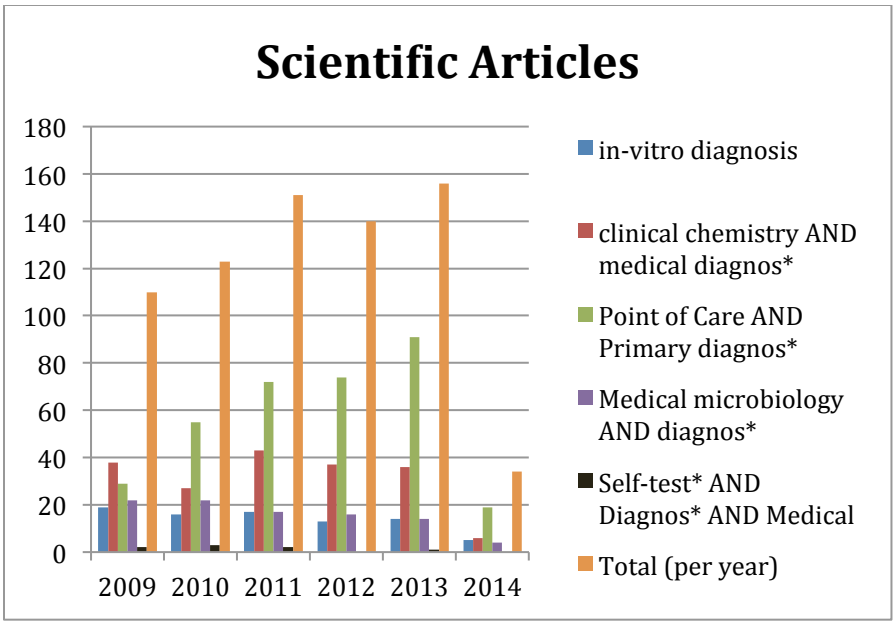

Figure 8. Scientific Articles analysis (worldwide)

2012-2014

The second period (2012-2014) shows fewer results than the first period, namely 331 scientific articles. Also in this period the search term 'Point of Care' shows the most results (184 results) followed by the search term 'clinical chemistry' (79 results). All search terms show fewer results in this period than in the first period except for 'Point of Care'. These results have increased every year, with a peak in 2013 (91 results). The search term 'Self-test' shows only one result in this period; in 2012 and 2014 there were no results.

In both periods many of the scientific articles of the search term 'in-vitro diagnosis' show a focus on a broad spectrum of diseases, technologies, methods and other diagnostic applications. An example is "Reliability of basophil activation test using CD203c expression in diagnosis of pollen allergy" in 2011, by Özdemir et al. (2011). The search terms 'clinical chemistry' and 'medical microbiology' show results focused on methods of testing, evaluation of tests, general diagnostic processes and case descriptions. The search terms 'Point of Care' and 'Self-test' show results for new (components of) devices, molecular labels for diagnosis, methods of testing, and other resources used for diagnostic related activities.

It can be concluded that there is a slight increase of published scientific articles for the search terms used in this research over the period 2009-2014. Again the Point of Care technology shows an increase every year. The clinical chemistry technology and medical microbiology technology shows a small decrease over the years. This gives the supposition that the area of Point of Care is becoming more interesting.

The function "Knowledge development" shows that the areas of research are mainly the PoC technology, clinical chemistry and medical microbiology. It is interesting to note that although the amount of both patents and scientific articles for PoC technology have increased every year (2009-2014), several opinions have been identified that show a negative attitude towards the development and use of this technology.

Function 3: Knowledge Diffusion

The results of the Knowledge diffusion in the Netherlands are shown in figure 9.
2009-2011

In this period many mergers or cancelled mergers between GP laboratories and/or hospital laboratories took place in the Netherlands. In 2009, for example, four hospitals in the center of the Netherlands merged their laboratories in order to create one "top laboratory". The four hospitals are the Universitair Medisch Centrum (UMC), het Diakonessenhuis in Utrecht, the Meander Medisch Centrum in Amersfoort and the Tergooiziekenhuizen. Also in 2010 a merger took place, and this led to the establishment of a laboratory by the Medisch Spectrum Twente and the Ziekenhuisgroep Twente. In this period also several network collaborations took place. In 2010, for example, several pharmacies were granted access to the data of the clinical chemistry laboratory of the hospital in Meppel. In 2011 GP laboratories (LabNoord and Laboratorium voor Infectieziekten) in the Northern provinces in the Netherlands merged, as well as the GP labs Medial and Atal. Other collaboration and mergers were that of Philips (manufacturer) and NEC (focused on pathology) in 2011, Future Diagnostics with companies from China and the collaboration between Future Diagnostics and Philips. But although these actors in the primary care system collaborate with each other, the dossiers are often developed separately from each other, which lead to unusable and difficult to exchange data between the actors. This affected the information exchange negatively between the different actors in the in-vitro diagnostic system in the Netherlands. This was stated by a Dutch clinical chemist/professor 'economical effects of laboratory diagnositcs'.

Respondent F showed the importance of the exchange of information in the primary diagnostic innovation system. This could reduce the amount of tests that are conducted unnecessary. But the interviewee also stated that the current technology already makes it possible for the GP laboratories to exchange information with every other kind of institute. The different perceptions of several actors in the in-vitro diagnostic system lead to difficulties in the information exchange process. Hospitals, for example, are in some case unwilling to make use of the data analyzed by GP laboratories. Sometimes the reasons are plausible. For example, various tests need to be up to date, because the values of the tests can fluctuate heavily. But sometimes the reasons are less plausible. The securement of a part of the diagnostic market by hospitals, for example, is one of the reasons why hospitals don't make use of the data analyzed by GP laboratories. Respondent E, however, stated that it was still difficult to connect different databases and systems with each other, and this difficulty is the reason why the information exchange between different actors in the in-vitro diagnostic is still laborious. This has especially to do with the fact that dossiers and information are transferred separately between different organizations. Respondent A showed that manufacturers already develop technologies that make it possible to connect the information system of laboratories, hospitals and GPs to each other and thereby enable proper information exchange. It was stated that the manufacturers also play a large role in this, because they have the power to implement these technologies and to advise their customers (laboratories etc.).

Knowledge has also been diffused in this period through conferences and other mediums. In 2010, there was a medical microbiology symposium in the Koninklijke Nederlandse Akademie van Wetenschappen (KNAW) -building in Amsterdam, which was organized by the Nederlandse Vereniging voor Arts-Assistenten Medische Microbiologie (NVAMM). In 2011 a workshop for clinical chemists was organized by several parties focused on the different roles, responsibilities and values about the upcoming PoC technology.

In the field of medical microbiology there have been international partnerships between laboratories in the Netherlands and laboratories in Hungary. Also medical students in Mozambique, as well as laboratory employees in Ghana, have been educated by Dutch laboratories.

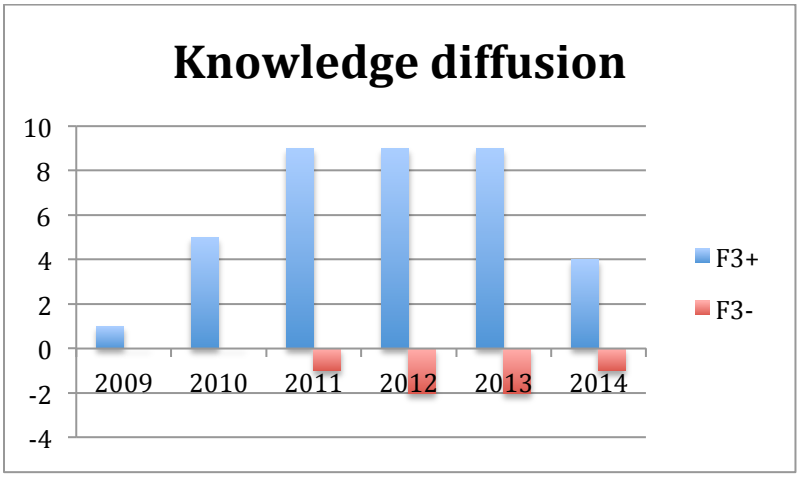

Figure 9. Function 3. Knowledge diffusion in the Netherlands

2012-2014

Also in the period 2012-2014 several mergers and network collaborations took place. The laboratory of the Rijnland Ziekenhuis (hospital), for example, was taken over by Medial (GP laboratory) in 2012. It was also reported that the exchange of information between a hospital (Jeroen Bosch Ziekenhuis) and Point of care labs (GP practices for instance) had intensified in 2012. This intensification refers to the automation of the patient data exchange between the hospital and the labs. Next to the mergers and collaborations between laboratories, also other actors collaborated in this period. In 2012, for example, several healthcare institutions, such as GPs and medical clinics, collaborated with medical-technology companies in order to improve the exchange of technology and knowledge. In the same year, the Isala klinieken (GP laboratory) collaborated with Philips Healthcare. In 2013, Roche Diagnostics has become responsible for the organization and management of the laboratories of LabWest. In 2014, Roche Diagnostics has established a partnership with the Santeon hospitals in the Netherlands.
In 2013, it was shown that GPs are constantly trained and educated in order to optimize the diagnostic process. This should lead to a lower request of additional diagnostic procedures.

In 2012 collaboration between the Jeroen Bosch Ziekenhuis (hospital) and Diagnostiek voor U (GP laboratory) was described as "not smooth". The reason was that half of the employees (specialists) of the Jeroen Bosch Ziekenhuis did not make use of the digital possibilities and thereby data of the GP laboratory. In the same year also a merger was cancelled. Two GP laboratories, SHL Group and Diagnostiek voor U, also decided to cancel the merger because of insecurity about the feasibility and value of the merger. In 2013, the merger between the GP laboratory Isala and the hospital St. Jansdal was cancelled. The merger was cancelled on medical terms without further explanation. In 2013 it was stated by the Dutch scientific professional association of laboratory specialists (Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde, NVKC) that the lack of proper collaboration between laboratory specialists and GPs (applicants) has a negative effect on the quality of diagnostics and will lead to unnecessary costs. This is to some extend in contrast with reports of the Saltro (GP laboratory), which state that the Saltro had strong ties in 2013 with the GPs concerning blood tests. They added that the Dutch hospitals are not able to develop such a logistic network

as the Saltro has with their participating GPs. Therefore partnerships between the Saltro with (regional) hospitals such as the St. Antonius Ziekenhuis and the UMC Utrecht took place.
In 2014, the largest GP laboratory of the Netherlands, namely the Certe group, increased its lab-activities by collaborating with the Universitair Medisch Centrum Groningen. The goal of the merger was to increase efficiency of the laboratories. In 2014 also several readings by the Isala Publieksacademie took place on the importance of blood tests and the developments in the technologies concerning blood tests. These readings are held several times a year. In 2014 it was stated, by an attorney and the director of the national association of primary care organizations, that the Autoriteit Consument en Markt (ACM) prevented companies from merging, without any further details on these companies. The ACM has the task to prevent the development of cartel situations by the use of fines for these types of collaborations. But this has led to regional collaborations in the healthcare system in the Netherlands not happening due to the fear of being fined.

All the interviewees emphasized the importance of consolidation in the laboratory market. The policy changes in 2014, as explained in the textbox "2015: A new way of funding the GP labs". This gives the laboratories more financial incentives to operate more efficiently. Respondent F showed that the revenues will decrease, while the operational costs will not decrease directly. It is therefore expected that in the short run consolidation will take place. Collaborations and mergers are more likely to happen than (hostile) takeovers according to respondent B and respondent E. The GP laboratories in de Netherlands are foundations and the hospital laboratories are part of the hospital. Foundations are not able to make a (hostile) takeover, but they can trade shares, merge or become part of the larger corporation. But as stated in the same interview, foundations are less quick-witted and have worse revenue models. Moreover, the GP laboratories are willing to merge, but not to give up their own company/foundation (companies name and culture). In a market where no organization is able to takeover (hostile) others and not willing to give up the company, mergers will barely take place. The events, however, show that mergers did take place. GP laboratories will probably merge with regionally partners. The laboratory market has a regional character, because of the 'prikposten' that have to be close to the patient and still be attainable for the GP laboratory to collect the blood samples. Partnerships between GP laboratories and hospitals will also take place more often, according to respondent E. Hospitals still rely on supply (patients, and patient data) from the first line, and collaboration can lead to lower costs. Also here, regional collaborations are expected, since the patients need laboratory research in the region to be informed as soon as possible. Although economies of scale, both on in- and output, are expected, at least operational efficiency can be reached through these (regional) partnerships. Operational efficiency refers to the improvement of information exchange, logistics and the reduction of unnecessary testing, which are expected to be the outcome of collaborations and mergers. This could lead to lower costs of diagnostics.
Foreign investment companies are not yet interested in acquiring Dutch in-vitro diagnostic laboratories, because the laboratories are not large enough (output, amount of tests conducted) which lower the expectations on profits. Respondents E does saw a change in mind set occurring, since the foreign investment companies are becoming more interested in the laboratories and keep an eye on the current changes in the diagnostic laboratory market.
Respondent F showed that the laboratory keeps close contacts with medical devices manufacturers such as Roche Diagnostics. This reason for this is to continuously improve and optimize the diagnostic process in order to reduce costs and turnaround times. Respondent A showed that the partnerships between (GP) laboratories and manufacturers become increasingly strategic also when consolidation takes place. The after-sales service and strategic consulting are of great importance for manufacturers to distinguish themselves from others,

instead of the diagnostic devices. The manufacturer can add value by advising the laboratories, acting as single suppliers (take care of everything) and looking at the long term. This leads to mutual dependence, since both parties rely on each other.
Respondent C stated that the health insurance companies do not collaborate with medical device manufacturers, but these suppliers become more interested in collaborating because of the developments and uncertainties with the PoC technologies.

The function "Knowledge diffusion" shows that in both periods (2009-2011 and 2012-2014) many collaborations and mergers took place, although the first period shows more network collaborations and the second period shows more complete mergers. In both periods these collaborations and mergers took place between mainly the GP- and hospital laboratories, although both periods also show that other actors such as manufacturers are involved in the knowledge diffusion process. Many partnerships were focused upon the improvement of data exchange. Interesting is also that in the second period more mergers did not take place, as it was also published in the same period that the ACM could be a barrier in the collaboration process.

Function 4: Guidance of the search

The results of the Guidance of the search in the Netherlands are shown in figure 10.

2009-2011

From the beginning of the period between 2009 and 2011 many studies have focused on the reliability and quality of PoC devices. In 2009 for example, three outcomes of studies were identified which were all focused on the quality of PoC tests. One evaluation showed positive results for a Vitamin B12 determination by a new PoC device, and one other evaluation showed positive results for a Hepatitis C determination. But a PoC device (HbA1 device) by Roche Diagnostics has been tested negatively. Not all negative assessment studies have focused on the reliability and quality of devices. One PoC device, for example, is unable to deal with emergency cases (so called Cito tests) but nothing is stated about the normal test results of this device. But it is also stated that there are too many uncertainties by the government concerning the upcoming PoC technology. These uncertainties were revealed in an assessment of safety related technological documentation items. Also standard setting issues were found, because PoC devices were in some cases only found at a hospital instead of GP practices. The reason for this was the unwillingness of the professional group of GPs to obtain the PoC devices in the guidelines. So the results in this period concerning the PoC tests show that although several devices were tested positively, there are several barriers. Next to uncertainties with the PoC technology, also self-testing technologies[8] have been assessed and the outcomes were negative. Two studies in 2010 also showed a negative outcome concerning the evaluation of several new PoC devices for HbA1. In 2010, a study showed that many tests used for self-testing are not reliable. Additionally, in 2010 there was not a standard (in the form of regulation) for the development and requirements of tests developed for self-testing. In this period, a Dutch ethicist has criticized genome testing. There is doubt about whether or not people are interested in knowledge about their potential portfolio of diseases they could suffer from in the future.

In 2010 a new standard for the reporting values for diabetes (HbA1c) has been introduced in order to improve the implementation of diabetes diagnostic devices. In this period several expectation about the market of primary diagnostic laboratories were made by a clinical chemist. The expectations were positive in a sense that fewer laboratories will lead to a more

[8] Self tests are tests that could be conducted by the consumers themselves

cost effective approach and higher quality of diagnostics. Differentiation, in the sense of type of diagnostic tests performed, and (partial) concentration could facilitate this. The link with technology is that developments in the clinical chemistry technology (and other medical laboratory technologies) could lead to economies of scale. But in order to get the benefits of these economies of scale, the laboratories need to be large enough (amount of tests conducted).

In the period between 2009 and 2011 also negative expectations on the technology or negative outcomes of studies have been identified. For instance, it was stated by a Dutch GP in 2010 that innovation in the healthcare in the Netherlands was held back because both policymakers and their advisers lacked the focus on technological developments. It was also stated in 2010 by a Dutch researcher (Jeroen van Roon) that GPs should not be granted more activities at the expense of hospitals, seen from a financial point of view. GPs should hire more employees and it could also lead to more and more diagnoses. This would then not lead to savings on the healthcare expenditures in the Netherlands.
In 2009 and 2010 some remarkable statements have been made about the reimbursement system in the Netherlands. It was stated by a manager of Wissenraet van Spaendonck (Organization specialized on partnerships) that a lack of communication between the College voor zorgverzekeringen (CVZ), de Nederlandse Zorgautoriteit (NZa) and DBC-onderhoud lead to barriers in the implementation process of new innovation in the health care and primary diagnostic system. The PCA3 test was an example of this. So standards for the reimbursement of new in-vitro diagnostic products were lacking. The slow process of being obtained in the reimbursement system makes it hardly possible to introduce new biotechnological tests. The lack of standard codes for the EPD has also been seen as a barrier, since this influences the automation (automatic data exchange) of the health care sector negatively according to a doctor's specialist in the Netherlands.

In the field of medical microbiology many articles were focused on providing technological guide. Lean management in the laboratories, for example, was explained in 2011 in the journal of the NVKC. Laboratories should apply a lean strategy and that should result in higher quality against lower costs. Technological guide has also been given on diagnostic procedures for certain diseases such as tuberculosis.

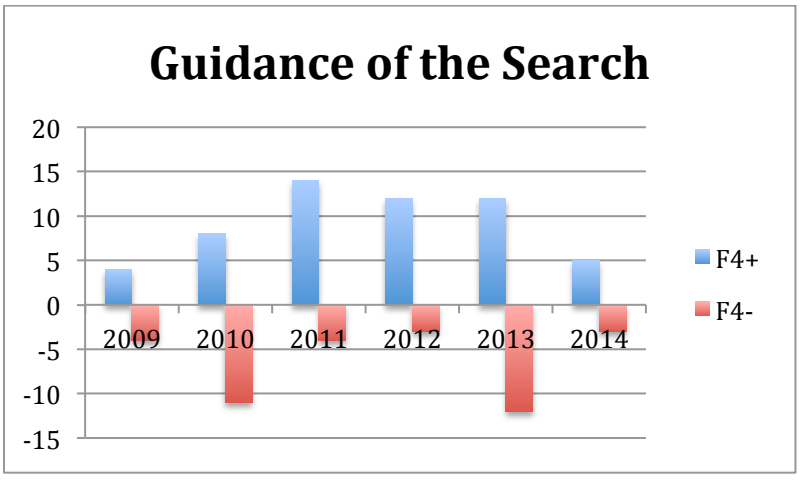

Figure 10. Function 4. Guidance of the search in the Netherlands

2012-2014

The transparency of the primary health care providers has been criticized due to the small scale of the primary care. The strategic consultancy company SIRM has published this in a research on the quality of the GP care in the Netherlands in 2012. Performance indicators and patient evaluations, for instance, are lacking in the primary care system. Also the consolidation process was of importance in this period. As explained in the textbox "2015: A new way of funding the GP labs", the NZa raised the first concerns about the primary diagnostic system and revealed their plans to change the reimbursement system in 2011. This has led to many events in the period between 2012 and 2014 reporting that consolidation will take place in the Netherlands. In 2012, for example, a manager at the Laboratorium voor Infectieziekten that in the future only five to seven laboratories will exist in the Netherlands stated it. This amount of laboratories is expected to be large enough to provide all patients with their diagnosis. It was also stated that a more efficient organization of the medical laboratory landscape would lead to a cost reduction of 200 million, although this has been mitigated by a different source in 2013. A spokesman of the SHL-groep (GP laboratory) doubts whether or not it will lead to a substantial reduction in costs while maintaining the level of service and quality. But in 2014, the merger of different laboratories into the Certe group resulted into a more standardized way of working. Through this standard setting, information exchange became less of a burden and thereby the chance of errors in the analyzing process also declined. So this example shows that mergers can lead to improvements in the primary diagnostic system through the use of standards for testing large volumes of diagnostic samples.

Respondent A explained that if both the laboratories and hospitals make use of the same devices (same manufacturers), that data exchange is possible and that the data is understandable by their receivers (for example a hospital). The hospital would then not have to conduct the same test again. This was verified by a director of a Dutch GP laboratory (Saltro) in 2013. She stated that if patients got their blood sampled at the Saltro (GP laboratory) and needed to go to the hospital afterwards, the hospital hardly made use of the data of the Saltro. The reason is that there is no interconnection between the IT-systems of both organizations. There are also concerns about the safety of the usage of ICT in the healthcare sector. In 2013 it was questioned why ICT should be granted such a large role in the primary diagnostic system. Privacy concerns and previous bad examples are the main concerns in these negative expectations. In 2013 a member of parliament showed that it was able to hack the EPD and thereby that the safety of using this IT system is too low.

The director of insurance company DSW labeled in 2014 the power of healthcare insurers as too high. The healthcare insurer has too much power according to this director, which would influence the quality of healthcare negatively. Small healthcare providers are for example, forced to comply with the conditions of the health insurers. The healthcare insurers are, according to this director, unwilling to negotiate about the tariffs, but force providers to comply with them. In an interview with respondent C, the power of the Dutch health insurance companies has been elaborated. Health insurance companies have a lot of information about the market and are therefore able to see opportunities to improve the system. Respondent C also stated that if no one puts any pressure on the laboratories and other actors in the system, no changes would be made at all. Due to the changes in the reimbursement of the GP laboratories, the health insurance companies will have the possibility to choose the most efficient laboratories. The expectation of respondent C was that this leads to mergers and collaborations so that these laboratories can reach economies of scale.

In this period several negative statements on the PoC have been identified. These statements refer to the absence of (quality) standards and negative results of the quality of devices. In

2013, it was shown in a research by the IGZ that the quality of use of PoC device at GP practices was not sufficient. There were no clear rules on the use of these devices, the devices were not monitored and recalibrated as they should and there was a lack of training for personnel to work with PoC devices. In 2014, researchers showed that the CRP devices (PoC) showed large margins of error after some time. Their study therefore showed the poor quality of these devices.
In 2013 a new diagnostic device (Biofire) for blood tests was approved with the CE-mark. The CE-mark acknowledges the quality of the new diagnostic product. In 2014, the expectations by experts showed that smartphones could be used as medical devices in the future, also for in-vitro diagnostics.

In the field of medical microbiology several attempts to standardization have been made. In 2012, a better standardization of the LYME-serology data handling between laboratories in the Netherlands in order to reduce the inter-laboratory differences was applied for because at the moment there was no standard for this. Also for several diseases, bacteria and viruses standards have been introduced in this period. These attempts to standardization were published in the magazine by the Nederlandse Vereniging voor Medische Microbiologie (NVMM). Standards have been introduced also in other field. Standards were proposed for diseases like whooping cough and how to organize the laboratories for this. In 2013 a quality surveillance program (MUSE) was introduced for medical microbiological laboratories. In 2013, a self-test to measure the C-reactive protein (CRP), for example, was not obtained in the guidelines by the NHG, because the health insurance companies did not reimburse this test. The health insurance companies were dure to this lack of standards not willing to reimburse the test because it was not obtained in the NHG guidelines. So there was a lack of standard setting for this specific device. Expectations on the self-testing technology in 2012 showed that these tests could prevent expensive treatments when a disease is detected too late. But the Huisartsengenoodschap (bond of GPs) stated in 2012 that self-testing only provides false security and therefore they show negative expectations on the implementation of this technology in the primary diagnostic market.

The function "Guidance of the search" showed that there were several negative assessment studies on the quality of the PoC devices/technology. There was criticism on a data exchange technology (EPD), and a proper reimbursement system (no standard setting) was lacking for new innovations. In both periods it was stated that there were activities of standard setting in the field of clinical chemistry and medical micriobiology. New in-vitro diagnostic products received a CE-mark in the period between 2012 and 2014, and there were positive expectations about the effect of consolidation of laboratories.

Function 5: Market formation

The results of the Market formation in the Netherlands are shown in figure 11.
2009-2011
Market formation has shown hardly any events regarding the formation of niche markets for in-vitro diagnostics or the other indicators in the Netherlands. But it did show that in the period 2009-2011 more and more laboratories had obtained new technologies in order to automate their diagnostic processes. This shows that there was market formation for the automation of laboratories. In 2011, before the merger into Certe group, LabNoord already installed a half automatic medical laboratory, which could analyze millions of tests per year. The Leids Universitair Medisch Centrum, a hospital had fully automated their bacterial (culture) research in this period. In 2009 it was stated that hospitals were more and more orientating on the

implementation of the EPD; as the title of the newspaper article was called: "Hospitals in the Netherlands wake up".
The costs of laboratory research have increased heavily over the years. The explanation, in 2011, for this increase was that the hospitals took over a large share of the laboratory testing market of the GP laboratories. Hospitals found out that these diagnostic activities were highly profitable and therefore competed with the GP labs. Although this led to higher costs for the insurance companies, it was a new niche market for the technologies central in this research.
It is also stated in 2010 that PoC will not be able to take over the laboratory market as stated by a scientific researcher. PoC devices are not expected to take over the laboratory diagnostics in, for example, hospitals due to considerations with regard to the quality, safety, logistics, costs and efforts regarding the use of PoC devices. This is seen in this research as a negative influence on the market formation in the Netherlands.

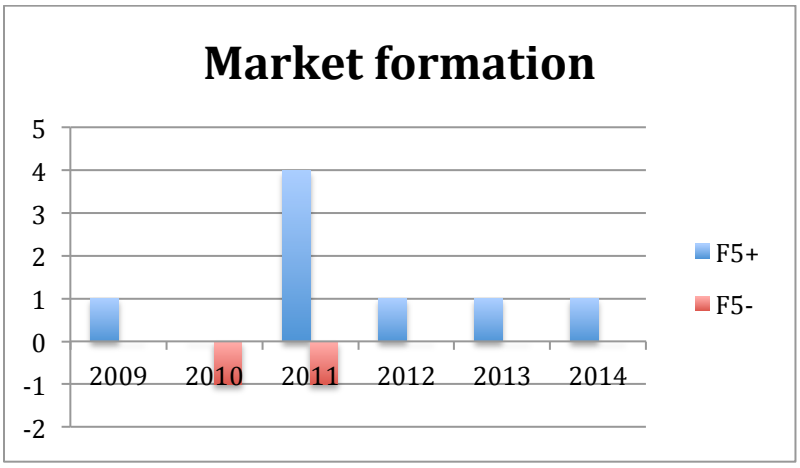

Figure 11. Function 5. Market formation in the Netherlands

2012-2014
In the period between 2012 and 2014 a project started with twelve GP practices that were granted the use of PoC devices for their diagnostic procedures. This enabled the GPs to conduct six different diagnostic procedures themselves. The results automatically were transmitted to the hospital systems and the GP systems. In 2014, a fast growing high tech company in the field of hybrid microscope technology stated that they already secured a niche market in the sense that several universities (Wageningen, Radboud) and hospitals (AMC Amsterdam, Rijnstrate in Arnhem), also companies such as Shell and Unilever were customers of the company. In 2013 a mediator, Medisch Coordinerend Centrum Omnes in Sittard, has prevented that 4.232 laboratory tests were conducted unnecessary. Although this has led to a reduction of diagnostics tests and thereby the use of in-vitro diagnostic technologies, it led to stimulating effects on the cost reduction in the primary diagnostic system.

Respondents E stated that one of the expectations is that the market structure will slightly change. They saw it as a possibility that in the future the "prikposten" would disappear and that blood (and other diagnostic) samples will be collected at and by the GP. GP laboratories or hospital laboratories could then collect the samples in order to be analyzed.

The function "Market formation" does not show clear trends, but does show that there is a market for almost all technologies of interest in this study. The market for in-vitro diagnostic tests, however, could be reduced because there is more focus on tackling the unnecessary diagnostic tests. Hospitals play a large in this because of the fact that they have indulged

themselves into the primary diagnostic market. This research also showed that there is hardly market formation for the PoC technology.

Function 6: Resource mobilization

The results of the Resource mobilization in the Netherlands are shown in figure 12.

2009-2011

In the period between 2009 and 2011 there was an investment by the Dutch government of 125 million Euros for research towards new applications of micro- and nanotechnology. This could imply applications for laboratories on the scale of chips with medical diagnostic purposes. Biocartis invested in the technological platform for the testing of human material. Biocartis acquired this platform from Philips. In 2011, the medical diagnostics company Agendia tried to gather 75 million Euros by selling through an initial public offering.

When looking at human capital, in 2010 it was stated that the availability of medical microbiological annalists could become alarming in the future. A shortage of specialists was foreseen in that year.

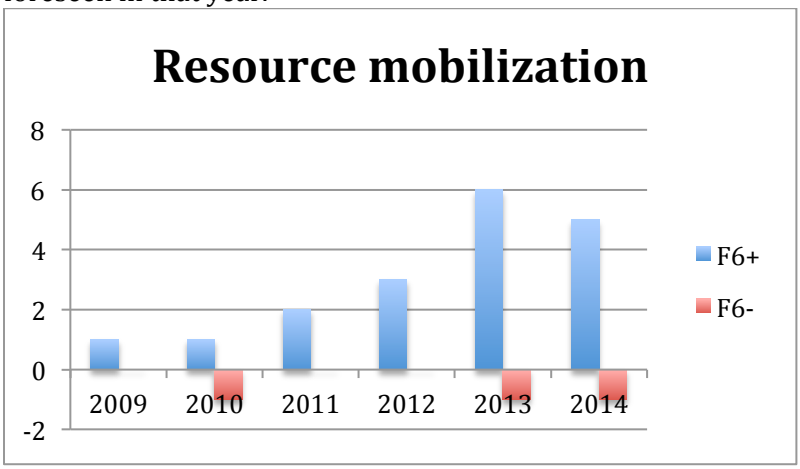

Figure 12. Function 6. Resource mobilization in the Netherlands

2012-2014

In this period many events show that more capital becomes available to the actors in the Dutch primary diagnostic system, through both mergers and investors. For example, in 2014 Achmea has created an investing fund together with the investment company Life Sciences Partners. This fund should stimulate innovations in the healthcare, so also in the diagnostic sector. When looking at the mergers, the difference with knowledge diffusion is that these events truly show that resources are mobilized. These mergers are not just mergers on paper, but the laboratories are truly combined, leading to a higher efficiency. The Saltro was also able and willing to invest in PoC devices (CRP) for their participating GPs. Subsidies from both the European Union and the Belgium government (respectively 1.5million and 6 million) made it possible for companies such as Cellsearch to develop their product. Cell search develops a product to identify types of cancer through blood tests. The subsidy by the European Union (EU) was meant for the development of a new, quick, AIDS test. In 2014, a manufacturer of medical devices, BD Kiestra, announced that the expansion of their premises was completed. Also in 2014, a GP organization and a hospital (Meditta and Laurentius Ziekenhuis) acquired a diagnostic center in a joint exploitation Ltd. It was also stated in 2014 by an investment banker that the medical technological producers (the manufacturers) are becoming more and more interesting for

investment companies. The reason is the relative short pay-off time for their investments and the relative stable market.

The changes in the reimbursement structure took place in 2014. As explained in the textbox "2015: A new way of funding the GP labs", the reimbursement structure for all types of laboratories changed to performance funding, and together with a recalibration of the tariffs, this has led to the fact that hospitals are no longer able to charge a higher tariff for the same diagnostic procedures. This is verified by respondent C. It was stated that the changes in the reimbursement of the laboratories equaled the field for in-vitro diagnostics. It makes it also possible for the Dutch health insurance companies to approach the various laboratories in the same way. But there still are some concerns. In this case these concerns relate to the PoC technology, because the healthcare insurers are only willing to reimburse the costs of the test, which is between the 3.3 and 5 euro. The consult is not reimbursed. This is illustrated as the negative event in 2013 in figure 12. This is confirmed by respondent C. At the moment there is no adequate costing structure for PoC testing. Respondent C also clarified uncertainties about the reimbursement of the PoC tests. In the Netherlands the use of PoC is experienced as more expensive than that of conventional laboratory testing. But if the order rate (asked by a laboratory for analyzing the sample) would be abandoned, PoC testing would cost less. Although, PoC testing could be performed by the GP, this order rate would still have to be paid to the laboratories according to the current reimbursement scheme. There is a good example where this is not the case; a PoC test for CRP. This case could act as an example for the other PoC tests.

In the Netherlands only a few events have been identified that showed investments made by laboratories or other actors in the primary diagnostic system. Respondent A explained that laboratories do invest in their diagnostic devices. The laboratories have to acquire the devices and also pay per test to the manufacturers. In some cases there are lease-contracts between the laboratories and the manufacturers. The expected consolidation process in the Dutch primary diagnostic system, however, is expected to influence the manufacturers, since the amount of buyers is decreasing. It could be that some manufacturers will not be able to stay in the Dutch market, or that the prices of the devices and tests for the laboratories will have to decrease. Also a shift to lease contracts could be a possibility. The latter option does not have to be detrimental to the innovation pace in the system, because laboratories then no longer have to account for depreciation costs. So although lease contracts are somewhat more expensive, the laboratories could be better able to adopt the newest technologies.

The function "Resource mobilization" does not show a clear trend, but does show that resource mobilization mainly took place through subsidies and investments in laboratories. However, there seem to be a shortage of human capital for the upcoming years. Also the reimbursement of PoC tests is still unclear.

Function 7: Creation of legitimacy

The results of the Creation of legitimacy in the Netherlands are shown in figure 13.
2009-2011
When looking at the creation of legitimacy, it can be noted that there are many lobbies in favor of the implementation of a system that could enable or improve information exchange between different health care providers. Again, the EPD is an example of this. In 2009, an advisory institution (Borghesi) advised several hospitals to implement the EPD technology and in 2010 the advantages of the EPD were explained in an article in a newspaper in the Netherlands. Also the Nederlandse Vereniging van Ziekenhuizen (NVZ) lobbied in favor of the implementation of

the EPD in 2011, because they believe that the information exchange between the different actors in the primary diagnostic system should be improved.

Concerning the developments in the clinical chemistry technology, the consultancy company BoerCroon lobbied in favor of looking at the technology. They state that the technology defines what happens in the health care industry and is therefore of importance to keep developing and supporting. In 2010, BoerCroon made a statement about the slow implementation of new innovations in the primary diagnostic system and health care in general. They stated that policy makers and their advisors do not have any focus on technological innovations. Next to policy makers and their advisors, also the health insurance companies have a great influence on the primary diagnostic system, as explained in a newspaper article in 2010. Health insurance companies are able to push (technological) developments by for instance only contracting those hospitals and laboratories that work the most efficient and thereby make use of the most efficient technologies. This is also verified by respondent C. In the same year Plexus, a Dutch consultancy company, showed through several financial analyses that the substitution of diagnostic activities in the second line to the first line (primary diagnostic system), accompanied with consolidation in the laboratory market, would lead to a reduction in costs for the Dutch primary diagnostic market of almost 700 million Euros.

Dutch GPs have lobbied for the development of one-stop shop (explained above) models for the GP practices in 2011. This would not only be beneficial for patients, but would also lead to quick and reliable diagnosis by the GP. Consolidation is what is lobbied for in order to reduce the costs of primary diagnostics. A different newspaper article states that diagnosis at a hospital should be paid, at least for some part, by the hospital itself. This article states that the bad functioning primary diagnostic market system is not only the fault of the healthcare insurers and insured, but also of the hospitals. In addition to this a different newspaper article states that more care should be transmitted to the first line (primary care/primary diagnostics) and the one and a half line (with which the GP labs are meant). The Minister of public health stated this.
In 2009 there was a lobby against the use of the "Chlamydia Handilab-C-test (PoC test), because the test was not accurate enough and therefore showed wrong results. This raised the question about the quality of PoC devices in general, and the NVMM stated that the use of PoC devices should be abandoned. Complementary to this negative lobby, in 2010, the RIVM released a report in which was stated that PoC technologies should not be used yet because they show too many insecurities. In 2011, there was some skepticism about the use of self-tests. Patient organizations and doctors are worried about the quality and enormous growth of medical tests for usage at home.

In 2011, the NZa releases two documents concerning the primary diagnostic system in the Netherlands. In these documents, one consultation document and an advice document, the NZa described the current (flaws of) primary diagnostic system in the Netherlands and gave advice to the Dutch government on how to improve this system. The NZa advised to change the type of financing of the primary diagnostics from budget funding to performance funding (explained below). Next to this advice, the NZa also made recommendation concerning the maximum prices (explained below), budgetary frameworks (the NZa advised to make use of a undivided framework, instead of the presence of several frameworks) and the NZa gave advice concerning the transparency of the primary diagnostic system. Transparency can only be achieved if the different stakeholders all apply to the same standards (of for example pricing) (Kamerbrief, 2013).

In the field of medical microbiology there was a lobby in favor of the continuing use of in virological culture techniques, instead of complete replacement by new techniques. A commission of the NVMM led the lobby, but the majority (83%) of the interviewed microbiologists were in favor of this lobby.

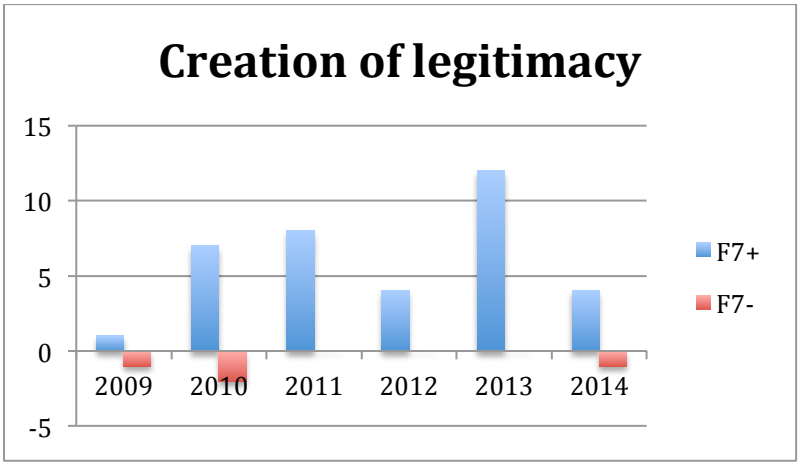

Figure 13. Function 7. Creation of legitimacy in the Netherlands

2012-2014

Also in the period between 2012 and 2014 lobbies were made in favor of technologies that enable the primary diagnostic system to become more efficient and of higher quality. Technological developments, in for example the clinical chemistry, could even lower the costs of primary care/primary diagnostics. A newspaper article stated in 2013 that a health insurance company in the Netherlands stimulated the development of several small laboratories into one or a few large laboratories. This is verified by respondent C. Growth in the primary diagnostic market is lobbied for because this could lead to a substitution of activities of the second line to the first. This was expected by the Minister of Public Health. BoerCroon, a consultancy company, lobbied for the integration of primary diagnostics and second line diagnostics in one of their online publications. This integration would be accompanied by better use of information exchange technologies, and would lead to a cost reduction of 20% because it would lead to a reduction of the amount of unnecessary tests.

In the period between 2012 and 2014 several lobbies in favor of the implementation of both PoC technologies and self-testing have been made. The Dutch GP association (Nederlandse Huisartsen Genootschap, NHG) lobbied in favor of improving several shortcomings of the use of PoC devices at the GP (as explained in the function 'Guidance of the search'). They stated that they will bring these shortcomings under the attention of the GPs. Home tests, which enable patients to do a test at home, were lobbied for in the sense that HPV-tests were expected to be used at home in 2 years (in 2013). In the field of medical microbiology there was a lobby in favor of mapping the possibilities and best practices concerning the diagnosis of Lyme disease. In 2014, there was a lobby against the implementation of the EPD, or systems similar to the EPD, in the Netherlands. A GP in the Netherlands, and chairman of the Dutch "Huisartsenverbond", stated that due to technological, organizational and substantial (possible) problems with the technology, it should not be implemented.

The NZa introduced several guidelines in the period between 2012 and 2014. In 2013, six guidelines were introduced in order to improve the funding systems, to elaborate on the new performance funding system, and to elaborate on the roles of actors in the primary diagnostic system. This latter focus refers to a guideline by the NZa in which it was stated that the Zorgverzekeringswet (Health Insurance Act) only determines what is obtained in the basic insurance, but not where the diagnostics are performed. In 2014, one guideline was focused on the transition model (and how laboratories could get refunding) and another guidelines was focused on the fact that there are maximum prices for all diagnostic activities, except for the diagnostic activities in the context of Modernization and Innovation (Modernisering & Innovatie, M&I). There are free tariffs for these latter activities. This shows that new innovative diagnostic procedures/activities are not bound by maximum prices. Respondent A stated that the manufacturers are not included in the decision making process by the NZa. The NZa has discussed their policy reforms with the Samenwerkende Artsenlaboratorium Nederland (SAN), care groups and other institutions, but without manufacturers, according to respondent A.

The function "Creation of legitimacy" shows that until 2014 there ware lobbies in favor of the use of IT systems such as the EPD, but in 2014 there was a lobby against the use of these systems. In the first the PoC technology was also highly doubted, but in the latter years the use of PoC does got the resistance as in the first years, on the contrary even because some lobbied in favor of the use of PoC in the GP practices. Consolidation was also stimulated. Consolidation will change the primary diagnostic landscape, as well as the relationship between the hospitals and GP laboratories, concerning the executor of the diagnostic analyses. A possible problem could be the lack of focus on innovation by the policymakers.

Performance

The Netherlands

In table 3 the indicators for the performance have been shown in the upper column. The Total Healthcare Expenditures (THE) are shown in millions (Euro), together with the In-Vitro Diagnostic Market expenditures (IVD mkt.). Also the percentage of the in-vitro diagnostic expenditures of the total healthcare expenditures is shown. The data show that the THE have increased between 2009 and 2012. Between 2009 and 2010 the THE have increased most heavily, and thereafter the increase of expenditures got weakened. Between 2009 and 2010 the IVD market increased with 1.94%, and thereafter the IVD market increased with 1.27%. So although the absolute numbers show that in 2010 the costs of the IVD market were higher than that of 2009, the increase in percentage was lower than the increase in percentage in 2009. After 2011 the costs of the IVD market decreased with 3.13%. The expenditures on the IVD market per capita show the same results.

When looking at the percentage of the IVD market of the total health care costs, it can be stated that the percentage decreased every year. In 2010 this decrease was the greatest, but in 2010 the total health care costs increased also the most (16.4%).

Table 3. Performance in the Netherlands

The Netherlands	THE (mil Euro)	% increase	IVD mkt (mil Euro)	% increase	IVD mkt/THE	IVD mkt/Capita (euro)	Source
2009	58775	5,93%	309	3,69%	0,53%	18,8	EDMA, 2009
2010	68413	16,40%	315	1,94%	0,46%	19,2	EDMA, 2010
2011	70153	2,54%	319	1,27%	0,45%	19,2	EDMA, 2011
2012	71984	2,61%	309	-3,13%	0,43%	18,5	EDMA, 2012
2013	-	-	-	-	-	-	-
2014	-	-	-	-	-	-	-

4.4 The German Healthcare System

In this chapter the German primary diagnostic system is explained. The purpose of describing the primary diagnostic system in Germany is to identify the relevant actors and their relationships in this system. In order to understand the primary diagnostic system, the health care system in general has been explained below and elaborated in Appendix I. Also the German primary diagnostic innovation system is analyzed by using the framework by Arnold and Kuhlmann (2001).

The German health care system rests on three founding principles, established by Otto von Bismarck in 1883 (Civitas, 2013). These principles are solidarity, subsidiarity and corporatism. Solidarity refers to the responsibility of the German government to take care of those who are unable to participate in the private health insurance sector and thereby securing universal access to health care (Civitas, 2013). "Subsidiarity suggests a decentralized system under which policy is implemented by the smallest feasible political and administrative units in society" (Civitas, 2013, p.2). Corporatism refers to the democratic character of the system; both employers and employees are represented (in groups and on the governing boards), on both the national and regional level (Civitas, 2013). The German system is suffering from a fragmented healthcare structure and this has led to very high patient volumes and healthcare provider contacts, as well as a surplus of healthcare providers offering too diverse service lines. The German healthcare system consists of the State, the cost bearer (Health insurance companies), service providers (Healthcare providers) and insurers (citizens) (Döring & Paul, 2012). The organizations report to the Federal Ministry of Health. The Federal Ministry of Health drafts laws, regulations and administrative provisions, but is also responsible for the supervision to the federal agencies involved and for appointing an expert commission in order to evaluate the development of public health (Döring & Paul, 2012). The State also directly funds facilities such as university clinics and state psychiatric hospitals. "The highest state authorities are the ministries of social affairs or health, to which, in turn, other state authorities, such as the state public health offices, report" (Döring & Paul, 2012, p.49). The public health offices supervise whether organizations such as health insurance companies are compliant with the federal and state laws. Municipalities enforce the legislations locally, focused on the

healthcare professions, distribution of foodstuffs and medical products, contagious disease prevention/control, and health education and counseling (Döring & Paul, 2012).

The German primary diagnostic process
The primary diagnostic process in Germany is to some extend similar to the process in the Netherlands. Fischer et al. (2008) described the diagnostic process in Germany. Also in Germany, a patient visits the GP because of (possible) health problems. The GP looks at the healthcare history of the patient and starts with the anamneses and physical examination. Thereafter the GP could choose for further diagnostic procedures. In this case, the patient has to donate diagnostic samples (such as blood), which are then analyzed by a laboratory (Gässler, 2012). The GP could thereafter come up with a diagnosis for the patient.

4.5 The German Primary Diagnostic Innovation System

This chapter gives an answer to the sub question 'What are the actors, networks and institutions in the German primary diagnostic innovation system?' In figure 14, the conceptual framework as given by Arnold and Kuhlman (2001), has been used in order to illustrate the German primary diagnostic innovation system. This section will briefly explain this figure. This has been elaborated in appendix J.

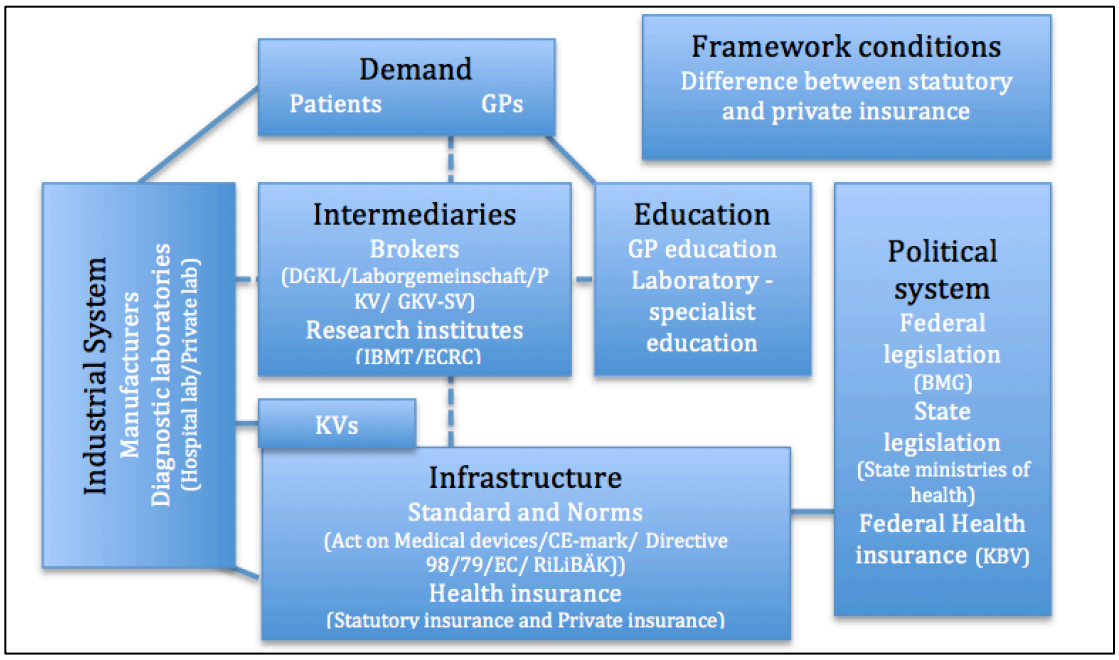

Figure 14. The German primary diagnostic innovation system

As for the Netherlands, also in Germany **Demand** refers to both patients as well as GPs. If patients are in need of medical care, they could visit every doctor they trust and who is certified to help the patient (BMG, 2013a). So patients are able to freely choose their *GP*. The German Federal Ministry of Health (Bundesministerium für Gesundheit, BMG) states that the GP has a central role in the health care system in Germany, with which is meant that the GP is the first point of contact for the patient and that the GP acts as a coordinator for further treatment (BMG, 2013a). This shows that it is the patient who can decide what kind of physician is the right one in order to solve their medical problem(s), instead of the GP (Linden et al., 2003). The patient even has the possibility to see more than one physician in order to seek for the optimal

solution (Linden et al., 2003). Respondent G has shown that the specialists are not located in the hospitals, as in the Netherlands, but most of them have their own practices locally. These practices could be located next to GP practices. It was also stated that blood and other diagnostic samples are taken at the GP office, instead of 'prikposten' in the Netherlands. The diagnostic samples (blood for example) are collected at the GP by a collection service of the private laboratories. The samples are then analyzed at the laboratories and the results are sent back to the GP. If blood is collected in the morning at the GP, then patients receive the results and their diagnosis at the same day. In Germany, the reinforcement of the rights and competencies of *patients* is an important concern for the health care policies (BMG, 2013b). An example is that representatives of patient organizations take place in meetings of the Federal Joint Committee (Gemeinsamer Bundesausschus, G-BA)[9]. There is also a staff function in the G-BA, which is primarily concerned with the needs of the patient (BMG, 2013b).

As for the Netherlands, the **Industrial System** in Germany is divided into the manufacturers of in-vitro diagnostic devices/supplies and the organizations involved in the collection and analysis of the in-vitro diagnostic process. In Germany the analysis of diagnostic samples can be executed at *private diagnostic laboratories* and at laboratories connected to hospitals (*hospital laboratories*) (Gässler, 2012). In Germany the analysis of diagnostic samples can be executed at private diagnostic laboratories and at laboratories connected to hospitals (hospital laboratories) (Gässler, 2012). The German private laboratories conduct their diagnostic tests far more efficient than other countries (VDGH, 2011). Especially in the field of clinical chemistry, the German laboratories are far more efficient. Diagnostic analysis can also be performed at hospitals. The market share, in terms of percentages of total health expenditures, is decreasing over time for the in-patient tests (hospital). The percentage of the outpatient tests (private laboratory) is increasing on the other hand (VDGH, 2011). Respondents G explained that fierce competition between the private laboratories resulted in highly efficient laboratory processes. Therefore the private laboratories are able to analyze the samples to lower costs than the hospitals. The result is that many hospitals mainly use their laboratories for emergency testing, and most other tests are outsourced to the private laboratories. In Germany, the umbrella organization for *manufacturers of in-vitro diagnostic devices* is called the Verband der Diagnostica-Industrie (VDGH) (VDGH, 2014a). The VDGH has 99 member companies, which account for approximately 90% of domestic sales in the diagnostic market (VDGH, 2014a). About 60% of these companies conduct research in Germany and almost 70% have production facilities in Germany (VDGH, 2014a). Respondents G showed that the relation between the manufacturers and laboratories is strong. This is because the laboratories become dependent on their supplier (the manufacturer) of the in-vitro diagnostic devices. The laboratories often lease the devices and often more than one device is used from a single manufacturer. Therefore it is less interesting to switch between manufacturers, because then several devices, which are part of a whole operating system, need to be handed in to the original manufacturer again.

The **Political system** can be roughly divided into federal legislation, state legislations, self-governing institution[10] and federal health. The BMG is the highest regulatory and supervisory authority (*federal legislation)* in Germany (MIPH, 2013). The core task of the BMG is to safeguard and further develop the statutory health insurances (SHI). Other activities are health, prevention and long-term care (BMG, 2014). Relevant Federal authorities belonging to the BMG are the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel & Medizinprodukte, BfArM), the Federal Institute for Disease Control and Prevention (Robert-Koch-Institute, RKI) and the Federal Institute for Vaccines, Sera and Blood

[9] The GBA will be explained below.

[10] An institution not controlled by outside forces

Products (Paul-Ehrlich-Institute, PEI) (BMG, 2014). The BfArM examines, inter alia, the safety of medical devices used for diagnosis (BfArM, 2014). The RKI is the central federal institution responsible for disease control and prevention (RKI, 2014). The activities of the PEI relate to the various duties laid down in German/European medicinal product legislation (PEI, 2014). Next to the BMG, there are *State Ministries of Health*, which are primarily concerned with the provision of health care by managing disease registries, prevention and the management of infection outbreaks (BMG, 2014). There are also relevant *self-governing institutions* present in Germany (MIPH, 2013). The G-BA specifies which services in the medical care are reimbursement by the statutory health care funds, and specifies measures for quality assurance of medical care for the patients (G-BA, 2014). The Institute for Quality and Efficiency in Health Care (Institut für Qualität und WirtschaftIichkeit im Gesundheitswesen, IQWiG) is an independent research institute that aims to objectively examine the (dis)advantages of medical services (MIPH, 2013). In Germany, there is the *Federal Health Insurance* (Kassenärztliche Bundesvereinigung, KBV), which is the political advocacy for office-based physicians and psychotherapists at the national level in Germany (KBV, 2014a). The main tasks of the KBV are the political representation of the interests of independent physicians at the federal level (KBV, 2014b). Other tasks are, inter alia, the representation of physicians to the health insurance companies, and the participation in the G-BA (KBV, 2014b). The KBV consists out of seventeen regional physicians associations (Kassenärztlichen Vereinigungen, KVs), spread across Germany (KBV, 2014c). Respondents G stated that the KVs have the budget for the reimbursement of the different types of physicians. So also for the in-vitro diagnostic system, the KV has the budget and divides this by power and size of the specialists groups. The KV has a list with the compensation tariffs for the diagnostic procedures and analyzes.

The **Intermediaries** are divided into research institutes and brokers. In Germany, several relevant *research institutes* can be identified. The Fraunhofer Institute for Biomedical Engineering (IBMT) is an institute where scientists conduct research in the field of, inter alia, molecular diagnostics, lab-on-chip technologies, and nanobiotechnology (Diagnostiknet, 2014a). At the Experimental and Clinical Research Center (ECRC) the scientists develop new strategies for diagnosis, prevention and also the therapy for different kinds of indications (Diagnostiknet, 2014a). One of the German *brokers* identified in this research is The German United Society for Clinical Chemistry and Laboratory Medicine (DGKL). The main goal of the DGKL is to represent, promote and develop the clinical chemistry and laboratory medicine in the area of research, teaching and health care (DGKL, 2014a). In Germany, there are also laboratory communities (laborgemeinschaft). These laboratory communities are defined as a community body of contract physicians which serves the purpose of providing medical laboratory analyzes in the same shared establishment (a laboratory) (Ministry of Finance, 2009). The private health insurance association (Verband der Privatenkrankenversicherung, PKV) represents the general interests of the private health insurances, the private health insurance companies (member firms) and thereby the interests of the private long-term care (PKV, 2014).

The **Educational system** shows that there are several educational organizations in Germany focused on primary diagnostics. Education programs are available to students to become GPs, laboratory specialists, and medical laboratory research (UKL, 2014; Bioscientia, 2014a; BMG, 2013c).

Infrastructure refers to the standards & norms, and health insurances. Since the healthcare market is highly regulated, health insurances play a significant role. In Germany, there is the Act on Medical Devices. The purpose of this act is "to regulate the trade in medical devices and, by doing so, to guarantee the safety, suitability and performance levels of medical devices as well safeguard the health and ensure the necessary protection of patients, users and other persons" (BMG, 2011, p.1). The medical devices will have to comply with the 'Directive

98/79/EC on In-vitro Diagnostic Medical Devices' regulation, according to a presentation of the Federal Ministry of Health of Germany (BMG, 2009). The CE-mark allows the products to be traded without restrictions on the Community market (BMG, 2009). Next to the Act on Medical Devices, there is the Act on Medicinal Products (BMJ, 2013). This purpose of this act is to ensure the quality, efficacy and safety of medicinal products in accordance with the following provisions (BMJ, 2013). The diagnostic laboratories have to comply with the Directive of the German Medical Association for quality assurance of medical laboratory investigations (Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen, RiLiBÄK) (BundesArztekammer, 2014). The *Health insurance system* is divided into the statutory health insurance funds and the private health insurance funds. Any citizen in Germany is usually compulsorily insured, which means that they are automatically covered by statutory health insurance (Deutsche Sozialversicherung, 2014a). The people who are compulsory insured, are in principle all workers with a gross pay that does not exceed a defined upper limit (in 2014 this was €4,462/month) (Deutsche Sozialversicherung, 2014b; Euroaxess, 2014).

Framework conditions refer to the financial environment, taxation and incentives, propensity to innovation and entrepreneurs and mobility (Arnold & Kuhlmann, 2001). The fee system for the GPs consist of a flat-rate annual fee, independent from the number of contacts, a flat-rate fee for extended treatments and a flat-rate fee for the treatment of chronically ill patients (UEMO, 2010). Statutory health insurance in Germany is financed through both the contribution of employers and the insured people (employees) (Deutsche Sozialversicherung, 2014c). According to respondents G, the laboratories send their bill to the KV and the KV reimburses the laboratory. The KV then collects the money from the health insurance companies. In the private insured reimbursement system, the patients directly pay the laboratory and thereafter collect their reimbursement from the health insurance companies. The Gebührenordnung für Ärzte (GOÄ) regulates the accounting of all medical services that are not covered by the statutory insurance system (Fairfekt, 2014)

Concluding remarks

This chapter has given an answer to the sub question *What are the determinants and interdependencies of the German primary diagnostic system?* The German primary diagnostic innovation system has shown that 'Demand' includes the patients and GPs, while the 'Industrial system' can be divided into manufacturers of in-vitro diagnostic devices and the hospitals and private laboratories. The patients get their diagnostic samples collected at the GP practices, which are then sent to the private laboratories to be analyzed. The political system can be roughly divided into the federal legislation (BMG), state legislation (for example the state ministries of health) and the Federal health insurance (KBV), which is a political advocacy for office-based physicians. The KBV can be divided into regionally KVs. These KVs hold the budgets for the GPs and other types of physicians. The health insurance system in Germany is divided into statutory insurance and private insurance, and both types of insurance lead to different types of funding the German primary diagnostic system.

4.6 The German In-vitro diagnostic Innovation System

In this chapter, the German in-vitro diagnostic technological innovation system will be explained. The in-vitro diagnostic technology refers to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). Since this research is concerned with improving the primary diagnostic system, the results described below are focused on the primary diagnostic system. All seven functions/key processes of the TIS approach are explained below. The time period will be divided into two periods, from 2009 to 2011 and 2012 to 2014, based on the release by the Dutch NZa of their official advice on the primary diagnostic system in 2011 (NZa, 2011b).

Function 1: Entrepreneurial activity

The results of the Entrepreneurial activities in the Germany are shown in figure 15.
2009-2011

In the period between 2009 and 2011 various diagnostic products and projects have been introduced and started. In 2009, a CE-marked molecular diagnostic test for the early detection of colorectal cancer in blood has been launched. In 2010, two German-based sister companies (IMGM laboratories GmbH and the Center for human Genetics and Laboratory Medicine) revealed their plans to use a new IT system for the joint development of robust and efficient workflows for targeted sequencing applications in the field of human genetics. In the same year, Bionerica Research installed a new Good Laboratory Practice (GLP) high tech lab. In this lab a new bacterial and viral real-time PCR method had been obtained for a more rapid detection of dangerous human or animal viruses. DiaSYS Diagnostic Systems, a leading specialist in the development and manufacture of high quality diagnostic systems, introduced a new quality management system for the laboratory market. In 2011, several PoC projects/products have been started/introduced. Radiometer, a German company, introduced a complete product portfolio that provides solution for requirements of PoC diagnostics, but also corresponding service, training and IT concepts. The university of Potsdam started a project in order to develop novel electrochemical biochips for POC devices to measure the protein level in blood. Siemens introduced the RapidPoint 500 Blood-gas analysis system.

Also several projects and products concerning information exchange and IT systems have been identified. In 2009, Rieco introduced an online-based communication platform with a focus on output management and order processing for medical laboratories. The MVZ Institute for Medical Diagnostics and CGM Germany have signed a cooperation to make use of the new ELAT software, which is a physician information system for the laboratory. In 2011, Bruker announced the successful completion of their new product, an integrated workflow by using the Bruker MALDI Biotyper for microbial identification from cultures and the BD Epicenter data management system.

Several products that were introduced or developed were accompanied by collaboration between various organizations in the primary diagnostic system in Germany. In 2009, for example, Bruker Daltonics announced a new project concerning molecular microbial identification, in collaboration with Synlab. In 2010, the Robert Koch Institute and Analytik Jena (manufacturer of analytical and bioanalytical systems) developed a complete new system for the detection of the new swine flu. In this period, also the larger companies such as Siemens (already mentioned above), Abbott and Roche Diagnostics introduced new diagnostic products.

But in 2010, it was stated by Roche Diagnostics, that their diagnostic chemical manufacturing and analytical services were expected to be discontinued in Mannheim. It was also expected that these activities would be transferred to Penzberg in Germany.

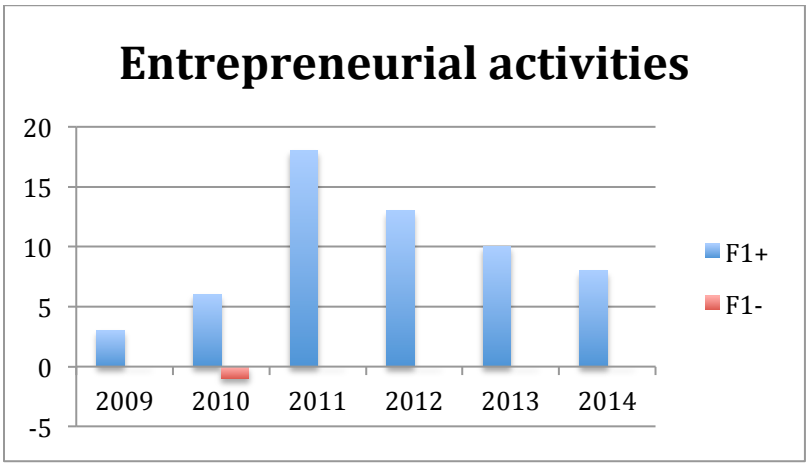

Figure 15. Function 1. Entrepreneurial activities in Germany

2012-2014

Also in the period between 2012 and 2014 various types of diagnostic products and projects have been introduced and started. In 2012, BIT Analytical Instruments introduced the HYRBID XL Analyzer in Germany. This device was the first hybrid analyzer for immunoassays and clinical chemistry. Research teams of both the University of Medicine Goettingen (UMG) and Chronix Biomedical developed a new blood test for the early detection of the rejection and damages as a result of transplantations of human-based materials (for example, organs). Although this product will probably not be used in the primary diagnostic market, it belongs to the in-vitro diagnostic technologies. In 2013, a new product (Dako Omnis) was introduced by the company Dako. This product provides complete automation and thereby meets the needs of large laboratories, hospitals and universities for automated "Advanced Staining " of tissue samples.

Several new PoC devices have been introduced, or projects have been started concerning the PoC technology. In 2012, a new PoC device for blood testing was being developed by the Fraunhofer Institute. In the same year the company EFK Diagnostics introduced two affordable PoC analyzers to the German market. Carpegen and Systec developed the fully automated real time PCR (Polymerase Chain Reaction) system (PoC device) named Gyronimo. In 2013 the Fraunhofer Institute presented a new optical rapid test for antibiotic resistance. In 2013 and 2014 also other PoC devices have been developed and/or introduced. In 2012, a system has been developed in the Marienkrankenhaus (hospital) to connect the PoC systems with the hospital information system (HIS). The period between 2012 and 2014 also shows other product developments or projects focused on the information exchange between the actors in the primary diagnostic system in Germany. In 2012, a videoconference system has been set up to link fourteen clinics in Germany and thereby to enable remote diagnosis. General practitioners were able to communicate with specialists through this system. In the same year new image-capturing software was completed which increases the efficiency of high-throughput processes for diagnostic analyses. This product increases the degree of automation and minimizes misdiagnosis.

Several products and projects have been developed through collaborations of companies. In 2014, for example, Pfizer collaborated with Siemens Healthcare to improve their technology concerning companion diagnostic tests. The other large diagnostic manufacturers such as

Roche Diagnostics, also launched new products. In 2013, Roche Diagnostics launched a new, fully automated laboratory solution to increase the efficiency and speed in the analysis of blood samples in medical laboratories. Siemens released a new labeling method in order to improve the data exchange and diagnostic processes from the GP to the laboratories.

Respondents G mentioned that the influence of technological development on the in-vitro diagnostic system is very important. These developments lead to more efficiency and automation. This means that more and more tests can be conducted with fewer employees. When looking at the large in-vitro diagnostic companies (Siemens, Roche Diagnostics, Beckman Coulter and Abbott Diagnostics, according to respondents G), each company specializes in different fields. The quality of all products is almost the same, but the companies distinguish from each other on turn around time of the tests, reliability of the tests, service and price. An example is Siemens that focuses on complete automation, as can be seen above, since Siemens is also developing a new labeling system.

The function "Entrepreneurial activity" shows that the entrepreneurial activities in Germany are focused on all kinds of activities, from new diagnostic products to data exchange technologies. The data exchange technologies range from technologies that enable data exchange between different organizations to systems that reduce errors in the diagnostic process. Interesting are the activities concerning data exchange in Germany. The reason for this could be that many large (international) companies have acquired several laboratories, so data exchange between the laboratories becomes more and more important; these laboratories are after all no competitors. Many projects or products introduced were also the outcome of partnerships between companies.

Function 2: Knowledge development

The results of the Knowledge development in the Germany are shown in figure 16.
2009-2011
In the period between 2009 and 2011 research projects were mainly focused on the identification and development of new methods of diagnostic, or new compounds/targets in the human body that can be used for diagnostic activities. In 2009 a research was focused on the potential of lgG antibodies that can be used for the diagnosis of celiac disease. In the same year also a new diagnostic approach using microarrays for gene expression was being studied. In 2009, it was announced that there is a center placed in Freiburg, where research takes place concerning the development of diagnostic tests for autoimmune diseases. This center belongs to the company Phadia Inc. Phadia Inc. is a worldwide leader in the development, manufacturing and marketing of complete blood test systems and founded in Sweden. These blood test systems focus on the clinical diagnosis and monitoring of allergies, asthma and autoimmune diseases. Research has also focused on areas such as a new diagnostic approach in oncology (2009, focused on endoprotease profiling with double-tagged peptide substrate). In 2010 a study was focused on developing a new basis for the reference measurement procedure for Hemoblogin A1c (HbA1c) determination. Other areas of research were Coronary Artery Disease, Acute Myocardial Infarction and Hemolyse. The focus of these projects was to identify new compounds used as markers in the diagnosis of diseases or to develop new methods of diagnostic testing. The use of microarrays and mass spectrometry as methods for diagnosis were central to several research projects.

Negative opinions have been expressed on the current technologies used for diagnostic activities. In 2010, negative opinions have been identified on liquid chromatography tandem–mass spectrometry (LC-MS/MS). This technology has become a standard tool in research

laboratories, as well as in clinical laboratories, but the critiques were focused on the inaccuracy of LC-MS/MS methods due to the process of ionization. Therefore the quality of this technology is being criticized.

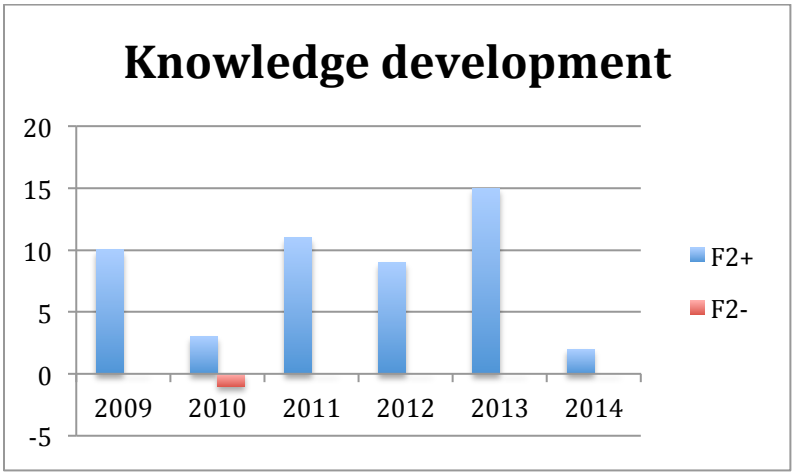

Figure 16. Function 2. Knowledge development in Germany

2012-2014

In the period 2012-2014 again mainly research projects in the field of in-vitro diagnostics have been identified. The focus of these research projects does not seem to be completely different form the first period (2009-2011). Microarrays are still a central subject for research, as well as mass spectrometry. Interesting is that many research projects focus on so called niches. An example is a research that was published in Clinchem[11], with the title "Increased Hemoglobin A1c in Obese Pregnant Women after Exclusion of Gestational Diabetes" focuses explicitly on obese pregnant women. The niche market relates to obese pregnant women, and the article focuses on the diagnosis of diabetes for this niche. Another example is a research focused on circulating epithelial cells in patients with Benign Colon Disease in 2012. But several other research projects are concerned with broader applications for diagnosis than niche markets as explained above. An example is the research that was published in Clinchem, with the title "Quality Markers Addressing Preanalytical Variations of Blood and Plasma Processing Identified by Broad and Targeted Metabolite Profiling". This research focused on metabolite profiling, which is a broad subject, since metabolites refer to intermediates or end products such as adrenaline, amino acids and glucoses. These intermediates and end products could act as markers to identify certain diseases. In 2012, a research project was focused on generating more knowledge on mass spectrometry. Although it was not stated where this research took place, it was written by an employee of the Max-Planck Institut für Biophysikalische Chemie. This project was specifically focused on the elucidation of the B-cell receptor-mediated signal transduction; a study towards proteomics in the human body. Proteomics is concerned with protein reaction in the human body and this could be used as starting points for diagnostic methods. Another research project was especially concerned with identifying markers for Alzheimer's disease in blood samples. In 2013 the Chief Information Officer of Roche Diagnostics (manufacturer) showed that companies such as Roche Diagnostic have bid data available on their patients, the diagnostic market and much more. This data is a source for improvement of the diagnostic system if used and analyzed in the proper way.

[11] International scientific journal in the field of clinical chemistry

The function "Knowledge development" has shown that there are research projects for all types of technology of interested in this research (in vitro-diagnostics, clinical chemistry etc.), but hardly any research projects in Germany for the PoC technology have been identified. It is also shown that the manufacturers posses a big source of data concerning patients, market information and more. This so called big data is useful to improve the primary diagnostic system.

Function 3: Knowledge Diffusion

The results of the Knowledge diffusion in the Germany are shown in figure 17.
2009-2011

In 2009 Synlab (medical laboratory) and Bruker (German manufacturer) announced a long-term partnership agreement in order to equip the laboratories of the Synlab with diagnostic devices of Bruker. Stratec, a German company specialized in biomedical system, and Abbott laboratories announced an agreement for collaboration in 2010. Several projects explained in the function "Entrepreneurial activity" started through partnerships. An example is the partnership between IMGM Laboratories and the Center for Human Genetics and Laboratory Medicine which started in 2010 in order to use a new IT system for the joint development of robust and efficient workflows for targeted sequencing applications in the field of human genetics. Another example of two companies collaborating in order to develop a new device is the partnership between Mtm Laboratories (a privately held diagnostics company with headquarters in Germany) and MetaSystems (a leading manufacturer of microscopic imaging systems worldwide). The goal of the partnership is to co-develop an automated imaging system for use in combination with mtm's CINtec® Cytology products. In 2010 a partnership between Abbott and the DGKL was focused upon attracting more and new laboratory personnel in Germany. One of the ways to do so was by introducing a new website where people should become motivated and active and to help them to pursue the career possibilities in the laboratory market. Different types of organizations (from manufacturers to laboratories) collaborate with each other in the German primary diagnostic system. The article "Innovative Produkte & Dienstleistungen für Diagnostik und Forschung" explained this way of working (through collaborations). The product complexity in the in-vitro diagnostics is very high present-day. The increased integration, through collaborations, of the biotechnology (and with bioinformatics and information technologies) offers promising opportunities for dynamic developments. So collaborating gives more opportunities to cope with the complexity of the in-vitro diagnostics. Mergers also took place in this period. In 2010, Fusion der Labore and Vivantes planned to merger into the largest hospital laboratory in Europe.

In this period also a lot of symposia, showcases and conferences (all labeled as conferences) took place in Germany. Every year there was the Medica conference, where all new (diagnostic) products/devices were displayed for the rest of the world. The Medica conferences take place in Dusseldorf, Germany. Another example is the International Federation of Clinical Chemistry and Laboratory Medicin (IFCC)-Worldlab conference, which took place in Berlin in 2011. The IFCC-Woldlab conference also takes place annually. The difference with the Medica conferences is that the IFCC is more focused on scientific knowledge diffusion, instead of product display. Respondents G mentioned that the Medica conferences are becoming less interesting for in-vitro diagnostics manufacturers. The costs of displaying are too high for the manufacturing companies. Most companies now show their products at scientific programs such as IFCC. At these types of conferences a link with scientific programs can be made, and the manufacturers act as sponsors of the conference. In return they can show their products, in combination with the scientific developments. Germany is too large for the manufacturers to visit their customers personally and show them their new products. The Netherlands is, according to respondents G,

not too large (geographical) and manufacturers are therefore able to visit their customer on a short notice. At the IFCC-Worldlab conference in 2011, Siemens Healthcare displayed a broad spectrum of its clinical diagnostic portfolio. This conference was focused on automation in the laboratory sector. Siemens therefore also showed products used for automation in the diagnostic process. In 2011, workshops took place by global initiative "Labs are Vital" in order to show the work and importance of medical laboratory activities.

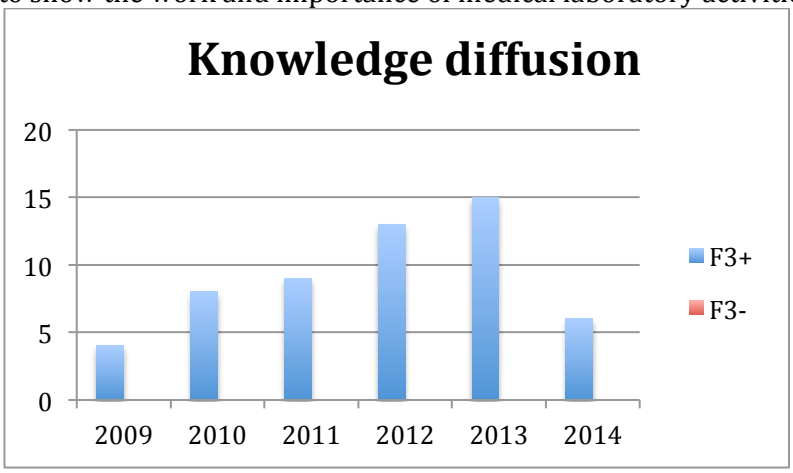

Figure 17. Function 3. Knowledge diffusion in Germany

2012-2014

In the second period (2012-2014) both partnerships and conferences (and similar activities) took place with the goal to diffuse knowledge between the actors in the German primary diagnostic system. Several partnerships took place. In 2012, a partnership between BIT Analytical Instruments and DRG Diagnostics took place in order to develop a revolutionary (as stated by the author) product; a fully automated and integrated random-access analyzer for immunoassays and clinical chemistry. A different partnership took place in 2012 between Sigma-Aldrich and Honeywell. Honeywell is a supplier of diagnostic services and analytical products and will provide Sigma-Aldrich with these products. Sigma-Aldrich is a manufacturer of biochemicals and organic chemical products. In 2013, a partnership between Siemens healthcare and Pfizer Inc. took place in order to develop diagnostic tests for therapeutic products in Pfizer's pipeline. Both companies belong to the largest pharmaceutical/medical companies in the world. Another interesting collaboration is the partnership between Ariosa Diagnostics, medical device company, and Sonic Healthcare. Sonic Healthcare has acquired several large medical laboratories in Germany. The collaboration makes it possible for Sonic Healthcare to provide patients with the Harmony Prenatal test. In 2013 the Diakonie-Krankenhaus Klinik (hospital) collaborated with a German medical laboratory called Bioscentia Ingelheim in order to make use of their laboratory activities.

Also in this period many conferences took place. As already explained, the Medica and IFCC-Worldlab conferences took place. Siemens showed in 2013 again its products focused on the automation of the diagnostic processes in laboratories. Next to this, there were several other showcases of new diagnostic products. In June 2012 there was a congress on the developments in the pathology sector. Since pathology is concerned with the origin and progression of diseases, this knowledge is important for the in-vitro diagnostic technology. It can be used to develop new devices for example. In 2013 a seminar concerning the newest PoC technologies took place. Interesting is that PoC is often mentioned in one sentence with near patient diagnostics. This shows that the benefits of the technology are focused on the patient. In 2013 the main theme of the so called "Generations College" (series of lectures provided for free by

the GenerationenHochschule) was Medical laboratory test. The goal was to show the importance of modern laboratory tests in the diagnosis and therapies of diseases.

Respondents G elaborated on the concept of information exchange (part of knowledge diffusion) between the different actors in the primary diagnostic. Respondents G mentioned that between most GP practices and private laboratories in Germany the data exchange is electronically and almost automatically. This means that the tests are labeled at the GP, then scanned and sent to the laboratory. No paperwork is needed, the data is just sent electronically to the laboratory and back to the GP's office. Currently the GPs are allowed to perform the simple diagnostic tests, such as diabetes, themselves and they can collect the reimbursement at the KVs. In practice this means that the GPs sent the samples to the laboratories, but collect the reimbursement from the KVs instead of analyzing it themselves due to the fact that the private laboratories do it more efficiently and therefore for lower prices. Respondents G mentioned that there is no digital data center such as an electronic health record (EPD in the Netherlands). GPs and hospitals do accept the data of tests of other GPs or laboratories in Germany, and as in the Netherlands in most cases the hospitals repeat the diagnostic tests in order to acquire up-to-date data.

The function "Knowledge diffusion" shows that in Germany many conferences, symposia and similar activities took place. Two large conferences, Medica and IFCC-Worldlab, have been identified and the manufacturers also show many of their products at these and other conferences. But knowledge diffusion also takes place through network collaborations in Germany. Not only similar organizations (for example two manufacturers) collaborated, but also different types of organizations collaborated with each other. Manufacturers of different types of products, but also private laboratories collaborate with manufacturers. Many partnerships are focused on the development of new products. This applies to both periods.

Function 4: Guidance of the search

The results of the Guidance of the search in the Germany are shown in figure 18.
2009-2011

The outcomes of the assessment studies on (new) in-vitro diagnostic technologies show, apart from the positive or negative outcome, that the diagnostic development is focused on the human genome and makes use of DNA or RNA sequences in order to develop a proper diagnosis. Also studies on new PoC applications were identified for this period. All these studies are conducted in Germany. In 2009, for example, a study has been identified focused on evaluating "Novel Flow Cytometry–Based Screening for Bacterial Contamination" (Dreier et al., 2009). In 2009 a device was tested positively that is able to detect circulating prostate tumor cells in the human body (Helo et al., 2009). In 2011 a study showed positive expectations on the diagnostic potential of saliva (Pfaffe et al., 2011). Some studies, however, also showed negative results. In 2010, for example, two studies on the diagnostic technologies have shown negative results. One of these studies was focused on a new PoC device developed for monitoring of coagulation. This product did not show positive results when tested. The same applies to a handheld (small device) echocardiography and point-of-care B-natriuretic peptide (BNP) measurement did not improve the GPs accuracy of heart failure diagnosis. Interesting is that in 2011 the studies increasingly focused on PoC devices, and these studies have shown more than once negative results. In the period between 2009 and 2011, several German laboratories got the approval to make use of medical diagnostic devices. Also several new products got the CE-marking. In 2009, Quest Diagnostics receive the CE-mark for their Swine flu test. In the same year, a product from Bruker, the MALDI Biotyper-Workflow, also receives the CE-mark.

Not all studies were focused on new products or methods. In 2009 there was a study that described the evaluation of the laboratory system in Germany. It showed that the German system ensures a high level of safety concerning the in vitro diagnostic medical devices. So this means that the diagnostic devices and diagnostic activities can be labeled as highly save in terms of incidents that were reported. But it was also stated that the current system (diagnostic system) could be further improved.

But in 2009, a journalist showed the insights of several doctors and professors in Germany about the role of the GP and this has shown some concerns towards the function of the GP in the diagnostic system. The conclusion was that the GP should think more economically and act according to this vision. Their practices should be organized as service companies and GP should be the service provides for their patients. The GP should act more as a gatekeeper. The GP should carefully consider what to do with the diagnostic procedures that are desired by the patients and whether or not these procedures are actual needed.

In the period between 2009 and 2011 doubt and uncertainty about the technologies involved in the diagnostic analysis have been identified. There is for example too much uncertainty at the German laboratories about all the possibilities and results of blood tests, as stated in 2011. In most cases the doubt and uncertainty are expressed by the opinions of researchers on new products/methods of diagnostic testing. In 2011 new standards of regulations were introduced for the in-vitro diagnostic system. These new standards require new standards for quality and competency of the medical laboratories in Germany, as used by accreditation institutions. This is seen as an extra burden for the laboratories in this research, although it is expected to increase the safety and quality of testing. In the same year also a project started to show the importance of laboratory testing in the primary care system. This was a global initiative by laboratories to improve the transparency about the role of laboratory diagnostics.

In the period between 2009 and 2011 several attempt to set standards took place. In 2011 new standards for medical laboratories were introduced in Germany. The DIN EN ISO 15189 standard was designed to improve the quality and competence of medical laboratories. As described above, there is much uncertainty about the possibilities and results of blood tests, so one of the professors in the newspaper article pleaded for increasing awareness regarding laboratory values described and what to do with this data. Next to the setting of standards, technological guide has been identified. In 2010, seminars were given by regulatory experts on how to cope with new regulations of, for example, laboratory accreditation (technological guidance). So the attendants were guided on how to cope with these regulations. Technological guide has also been given, in 2011, to physicians in Germany on what they should know about diagnostic testing. The understanding and usefulness of particular diagnostic tests have been instructed to these physicians.

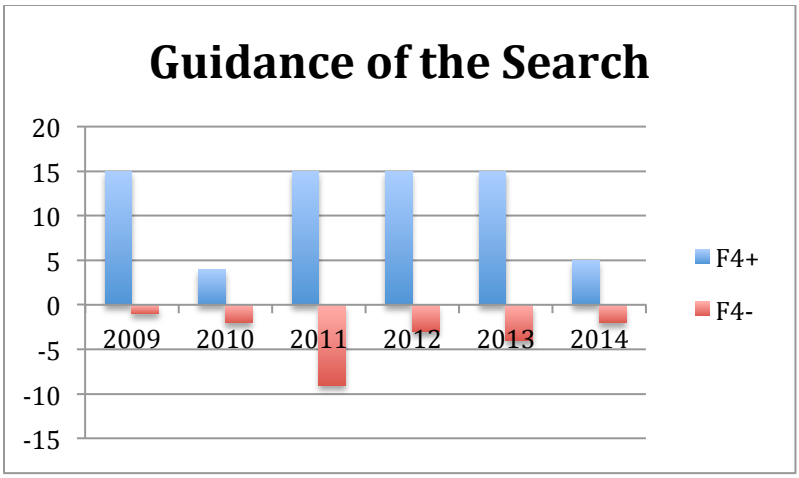

Figure 18. Function 4. Guidance of the search in Germany

2012-2014

In 2012 positive expectations by scientists were made about the promise of new angiogenic markers for the identification of preeclampsia. There were also positive expectations made on the importance of IT systems and programs. These IT solutions refer to, for example, electronic patient systems and Point of Care quality assurance networks. These systems are hardly indispensable anymore in the German system. In 2012 there re positive expectations about the use of an online cloud (database) for the storage of data such as patient data. With this is meant that data about the patient is stored online, which makes it possible for all relevant actors in the system to access the data. Although problems are expected when using online databases for these purposes, it is expected by a director of a laboratory in Germany that these problems can be solved. Other expectations on data exchange in 2012 referred to the availability of a knowledge base and thereby the possibilities of improving the diagnosis of diseases since all knowledge about the human being could be stored in these databases.

In 2012, it was stated that new regulations (The Medical Devices Directive, MDD and the guidelines of the German Medical Association) required laboratory personnel to be trained and educated in order to be able to work with PoC devices. This can be seen as an extra burden for the personnel. But on the other hand, a product was approved that enabled the personnel to make use of e-training to meet the new requirements. In 2013, a doctor in Germany expected that the future of PoC devices is highly positive. In the same year a new PoC device was granted the CE-mark and was therefore ready to be commercialized. Technological guide has been given in 2013 for the process of discovering diagnostic markers for personalized medicine through diabetes subpehnotypes and metabolomics.

In 2012 there were concerns about the turnaround time of the diagnostic samples and analyses. A limiting factor for the appropriate use of in vitro diagnostics is often the availability of the data analysis. This is because after sampling at the GP, the sample has to be sent to a medical laboratory. After the sample is analyzed, the results are sent to the GP, but this takes some time. Another concern, as shown by an event in 2014, was about the privacy. This has become an important point, because data exchange becomes more and more important in Germany. The reason for this is because more and more laboratory activities are being outsourced by hospitals (explained in "Resource mobilization"). So there is especially uncertainty about the quality of privacy and confidentiality of the patients when, in particular, the hospital laboratories outsource their laboratory activities to a higher extend.

In 2014 the VDGH members explained the positive and negative characteristics for the manufacturing companies in the primary diagnostic system in Germany. The high qualification of the staff, the good payment and the fast market approval (CE marking) were perceived as positive characteristics. The negative characteristics were the price pressure in the market, the low level of reimbursement in the fee schedules as well as the consolidation and concentration on the customer (laboratories) side. In the same year it was expected that the PoC technology and devices will be a good complementary to the laboratory analysis in the future.

The function "Guidance of the search" shows that the in-vitro diagnostic technologies have been intensively studied regarding their performance and quality. The PoC technology has become more and more important, but has also shown many negative outcomes. Standards have been set in both periods, but also several uncertainties and concerns were notable. The data analysis process and the possibilities of diagnostic methods (blood tests) were the main areas of concern. Guidance of the search has also shown an evaluation of the primary diagnostic system and thereby negative characteristics as experienced by manufacturers.

Function 5: Market Formation

The results of the Market formation in the Germany are shown in figure 19.
2009-2011

The PoC technology market is perceived as one with high potential. It is, for example, expected by several experts (professors at universities) that the PoC technology will be able to take over a part of the in-vitro diagnostic market. Another example is that PoC devices are more and more used in clinics. The 'Park-Klinik Weißensee and the Schlosspark-Klinik are examples of clinics in Germany that already have adopted PoC devices. The result is that patients now only have to wait three minutes in order to get the results of their blood glucose monitoring. The PoC technology has also found a niche market in the hospitals. It was stated that the hospitals form a platform for PoC devices and that PoC devices will be increasingly used in hospitals. Also the emergency diagnostics (diagnostic tests that have to be conducted immediately) appear to be a niche market for PoC devices. IT systems have found a market in the medical laboratories. The reason for this is that companies that merge will need these systems to interact between the merged or acquired laboratories. They expect to gain from this efficiency in management and state that the level of security of these IT systems is sufficient. Abbott Laboratories introduced such an IT system. Abbott launched a new web based integrated laboratory informatics system in order to help laboratories to operate more efficient and productive while minimizing errors. IT systems will also become more important with the further development of the PoC technology, since more data exchange will be needed, and the consolidation of the laboratory market. Consolidation will lead to higher volumes of testing and proper data handling and exchange will be needed for this. But in 2009 a professor in Germany stated that there are too many unnecessary tests conducted in the medical clinics in Germany. This excessive use of the laboratory tests influences the budgets of the hospitals, but also leads to more follow-up studies and a higher burden for the patients.

In 2010 it was mentioned by a spokesman of the association of private health insurers that private insured Germans receive far more diagnostics than the statutory insured Germans. This leads to increase healthcare expenditures in Germany. So although the diagnostic market for privately insured Germans seems to be rather large, it is perceived as a barrier since it leads to higher costs of the primary diagnostic market. In 2011 several professors in Germany stated that the market of the traditional diagnostic analysis will not be replaced completely by the PoC technology. This can be seen as detrimental in the implementation process of the PoC technology, since it shows a smaller potential market for the PoC technology.

An IT-specialist perceived the amount of IT systems in the German primary diagnostic system as too high in 2011. These IT systems, such as hospital information systems, operate as isolated islands, and the consequences are media breaks (problems with data exchange). Patient data has to be entered more than once, resulting in higher costs, more time spent and poorer data quality. This shows that the market for IT systems cannot handle too many different types of systems.

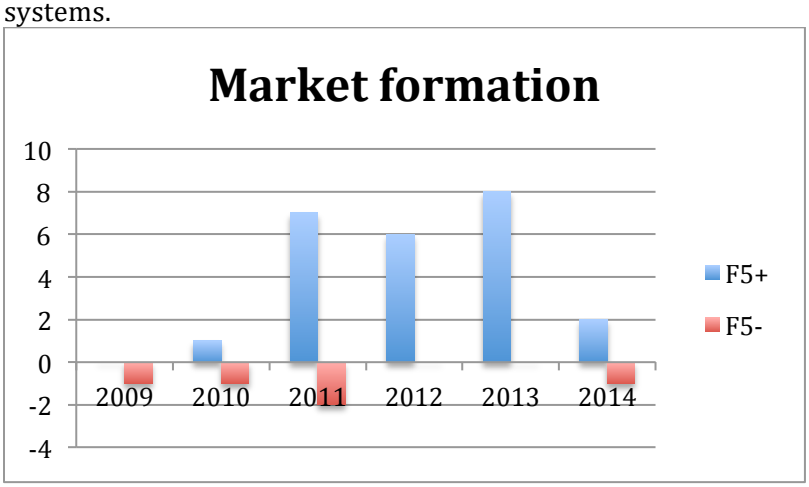

Figure 19. Function 5. Market formation in Germany

2012-2014

In the second period, also market formation activities for the PoC technology have been identified. It was stated in 2012 that already 2000 nurses in German hospitals make use of PoC devices. In the same year it was reported that the PoC technology had proven itself in the emergency department of hospital in Frankfurt. In 2012, True Diagnostics was actively seeking for distribution partners in Germany for their PoC test focused on specific hormones of the prostate. In 2012 it was also stated that no other area has such a high degree of standardization, automation, IT-structuring and quality insurance as the medical laboratory sector. In 2012 an implementation project started at the Fraunhofer Institute. This project was focused on the use of a new system that could measure up-to 500 different parameters in less than 15 minutes. The project was called the Fraunhofer IVD Platform. Also niche markets for polymerase chain reaction (PCR) tests were developed. PCR was, for example in 2013 already used for 1000 patients at a university. Interesting is that many data exchange related (niche) market formations were identified in this period. IT has been used more and more in hospitals, but also for PoC technology. But in 2014, there were negative sounds concerning the distortion between the compulsory insured patients and the private insured patients. It was stated by a German journalist that the private insured patients were going through many unnecessary and expensive diagnostic tests when they would visit a GP. It was also stated that this is also in the interest of the doctor, financially seen, because the GPs could earn some extra money through the description of these extra diagnostic tests.

Respondents G showed that PoC is partly used as a substitute for a complete in-vitro diagnostic laboratory in Germany. PoC devices are hardly used at GPs because the costs per test are lower at the private laboratories. So the tests are just forwarded to the private laboratories by the GPs. Most of the diagnostic tests of hospitals are still sent to the private laboratories, since they are more efficient. PoC devices are increasingly used for the most necessary tests or emergency tests in hospitals. PoC technology is able to provide the physicians in a short time with an analysis of the diagnostic samples, but it does need manpower to operate the devices (in

comparison with one complete automated laboratory), training is needed for the personnel and the devices need to be monitored. Also the quality is still somewhat doubtful, but the quality is increasing according to respondents G.

The function "Market formation" shows that there are clear (niche) markets for both the PoC technology and technologies concerning information exchange. It was even shown that the markets are combined for these technologies. But both periods also show that there is distortion in the markets for the private and compulsory insured people in Germany. The private insured people receive far more diagnostic tests and this increases the expenditures in the primary diagnostic market.

Function 6: Resource mobilization

The results of the Resource mobilization in the Germany are shown in figure 20.
2009-2011
In the period between 2009 and 2011 many take-overs of medical laboratories in Germany took place. Sonic Healthcare, for example, is an Australian company who bought or attempted to buy several laboratories in Germany in 2009. Labco, another international player in the medical diagnostic market, has also acquired several laboratories in Germany in 2009. Another large player, BC partners, stated in 2009 that it was looking to acquire laboratories in Germany in order to take over a part of the market. Consolidation of the laboratories would be a part of this process, meaning that in the end, less and less laboratories remain. Next to international acquisitions there were also acquisitions by German diagnostic organizations. In 2010, for example, Millipore, a supplier of pure water system, laboratory and production equipment, was bought by Merck (international pharmaceutical company. Also the merger of Thermo Electron with Fisher Scientific is an example of an acquisition in the laboratory market and on the same time an example of the consolidation process in the laboratory market. Next to the laboratory market, also the manufacturers of diagnostic devices made investments in the form of acquisitions. Roche and Siemens have both made acquisitions of diagnostic companies in 2011. Roche had bought PVT Probenverteiltechnik and PVT Lab systems, while Siemens had acquired Bayer Diagnostics and several other companies outside Germany.

But on the other side, one of the attempted investments to generate the largest hospital laboratory in Europe (between Charité and Vivantes) did not go through in 2010 and was put on hold. The reason was that there was no consensus among the board of directors; half of them voted in favor of the merger and half voted against. Further research has shown that the merger did go through eventually in 2011 (Charite, 2014). In 2011, it was stated by a representative of the Verband der Diagnostica-Industrie (VDGH) that there is an absence or delayed acceptance of innovative practices by the statutory health insurances (SHI) because of unreasonable high demands on user testing health economic studies. In short, this leads to problems of reimbursement for newly developed diagnostic devices and tests in the field of near-patient laboratory diagnosis. In the same year also the problem of the disappearance of laboratories in hospitals was revealed. More and more (smaller) hospitals combine their laboratories, but this has negative effects on the turnaround time of testing, since it will take longer to get the results.

Respondents G elaborated on the consolidation processes in the in-vitro diagnostic system in Germany. In Germany many laboratories have been acquired by large international venture capitalists. Germany was highly interesting for these companies because there was already (fierce) competition between the private laboratories. In Germany, the private laboratories were founded strictly for business and focused on generating profits. Most of the laboratories are GmbHs (Gesellschaft mit beschrankter Haftung; Private company limited by shares). This

made the German private laboratories very efficient and led to low costs per test. But this fierce competition also led to more and more consolidation of the private laboratories in Germany. When the first laboratory became acquired by a large international venture capitalist, there was no market leader. These laboratories were bought to develop them into the market leaders. The type of tests (blood tests, medical microbiology etc) were assigned per laboratory in the most efficient way in order to increase the amount per type of tests and increase economies of scale. So next to the fact that multiple laboratories were acquired, also the types of tests were assigned in the most efficient way to increase economies of scale. This would then give these groups of laboratories more and more buyer power, so lower prices could be bargained for at the suppliers of the in-vitro diagnostics. This was an incentive for the other laboratories and laboratory groups to consolidate. According to respondents G consolidation also took place between the manufacturers, such as Roche Diagnostics, and the hospitals in Germany. Hospitals are not large enough anymore to analyze the diagnostic samples as efficiently and for the same low costs as the private laboratories. Also the hospitals experience fierce competition, in contrast to the Netherlands, creating incentives to work as efficient as possible. The hospital laboratories also receive not as many patients as in the Netherlands, because only the patients that need to be hospitalized are in the hospital in Germany. In the Netherlands, also the patients that have to visit specialists go to the hospital, but as stated, in Germany the specialists, such as urologists, mostly have their own private practices. Therefore the hospitals will not perform the same amount of tests as the private laboratories, which reduces the economy of scale and return on investment. As a result the (smaller) hospitals outsource more and more of their activities. Also most of the laboratory tests are outsourced to the private laboratories; only the tests for emergency cases are conducted at the hospitals.

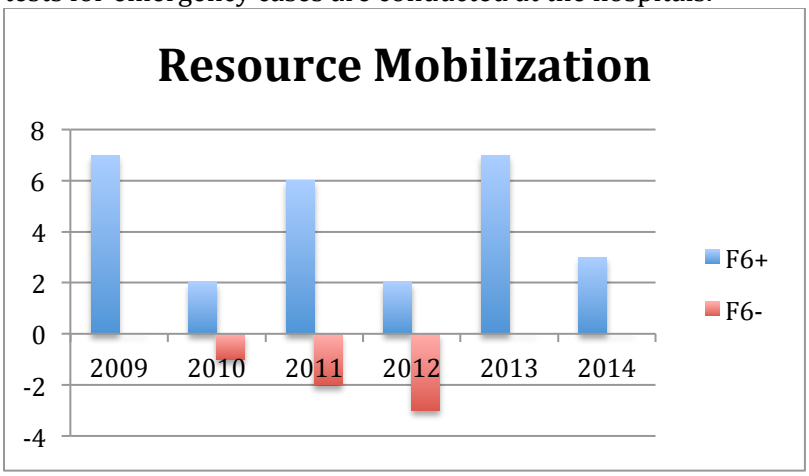

Figure 20. Function 6. Resource mobilization in Germany

2012-2014

In the second period also many acquisitions by venture capitalists took place. Sonic Healthcare, for example, has bought the laboratories of Labco in Germany in 2013. Labco is a different large investor in medical laboratories. Interesting to note is that the acquisition went through for 76 million Euros. In 2014, the acquisition of five pathology laboratories from Labco by Sonic Healthcare was also completed. Leico Biosystems has acquired Kreatech Diagnostics in 2013. The reason for this acquisition was to acquire the portfolio and expertise of Kreatech Diagnostics.

In 2014, the compu-group Medical bought Swiss Vision4health. The company's core product was a laboratory IT system together with a diagnostic portal. This portal supports services between healthcare providers and medical labs. Investments were made by laboratories to improve their products and processes. The university laboratory of the university of Bonn, for

example, has invested in their research in 2013. Roche has invested in a new complex called the "Diagnostic Operations Complex II" in 2013. Roche invested 200 million Euros in this project. Investments in new products or R&D projects have also taken place in this period. In 2013, 75 000 Euro was invested in a project about Alkaline Phosphate. This enabled the scientists to conduct research in this field of knowledge.

In 2012 it was stated that the university hospital in Aachen entrusted its entire laboratory diagnostics to a commercial supplier (private laboratory). Although this will lead to reduction of costs on at least the short term, but revenues from diagnostic testing are also abandoned.
But in 2012 it was shown that outsourcing is only possible and a viable strategy for smaller laboratories. But otherwise the strategy will only influence the laboratory negatively. Also in light with the previous statements about the outsourcing of laboratory activities by hospitals, this could be detrimental to the education and training of new laboratory personnel. This is also a problem stated by a medical director of a private laboratory (Synlab) in 2012. He stated that there is a lack of young people among the medical laboratory. Human capital can therefore be seen as a barrier in the implementation process of the in-vitro diagnostic process.

Respondents G discussed the presence of the large international investment companies such as Labco and Sonic Healthcare in Germany. As stated above, due to the fierce competition between the private laboratories, they became highly efficient and therefore interesting for the venture capitalists to be acquired. But the interview showed that next to the acquisitions of the laboratories, the investments in the in-vitro diagnostic do not have to be that high. An example is the Diakonissen-Stiftungs-Krankenhaus (hospital) in 2012. It received new laboratory equipment and computer equipment at virtually no costs due to successful negotiations with the manufacturers. According to respondents G, many German laboratories signed contracts with manufacturers in order to lease diagnostic devices instead of acquiring the devices. A minimum number of tests is required, because in many cases the manufacturer gets paid per analysis by the laboratories. Most hospitals are therefore not able to get such agreements, because their number of tests is too low. Next to the advantage of lower investments, the laboratories do not need to write-off their devices, as is the case in the Netherlands. This provides better possibilities to adopt new devices when they are developed. Loss-making hospitals are, next to laboratories, being acquired by venture capitalists in order to improve the business and sell them in the future. As stated, at this moment, hospital laboratories are mainly used for the most simple and necessary diagnostic tests. But one of the solutions is that some hospitals are trying to attract more and more specialists to the hospital, just as in the Netherlands. This would increase the amount of patients, and could increase the amount of tests; thereby making it profitable for hospitals to invest in diagnostic devices

The function "Resource mobilization" showed that the Germany laboratories are highly of interest for large international companies that are willing to invest. In both periods, large international companies such as Labco and Sonic Healthcare have acquired laboratories in Germany. The reason is that the German laboratories work extremely efficient. On the other hand, hospitals are increasingly outsourcing their laboratory activities to private medical laboratories. Financially this could be beneficial for hospitals on the short term, but there will also be negative effects on the training and education of laboratory personnel. The absence or delayed acceptance of innovative practices by the statutory health insurances could also be detrimental to the innovation processes of the primary diagnostic system.

Function 7: Creation of Legitimacy

The results of the Creation of legitimacy in the Germany are shown in figure 21.

2009-2011

In the period between 2009 and 2011 lobbies for/against mergers and collaborations have been identified, and also lobbies in favor of implementing more innovations in the laboratory diagnostic system were found. In 2009, the large international company Sonic got approval for the acquisition of a medical laboratory in Germany. As explained, Sonic has acquired several laboratories and even bought another large group of laboratories named Labco, one of the largest groups of laboratories in Europe (Knipp, 2011). This approval is seen in this research as the creation of legitimacy towards the acquisitions of laboratories and therefore the consolidation process in the German primary diagnostic system. In 2011, Sonic did encounter some difficulties in the German laboratory market. The reason for this was that in Germany the focus on short payments by the statutory health funds was in dispute at that moment. But the concerns were only small and were not expected to have any impact materially on margins.

The privately insured patients in Germany receive far more diagnostic tests when they visit the GP and thereby increase the costs of total diagnostics in Germany. More importantly, is that these tests are often unnecessary, so these tests will not contribute to cost reduction in the further healthcare process. A lobby against this overuse was therefore made by the Ex-president of the Berlin Chamber of Physicians in 2009.

In 2010 there was a lobby from the German government to increase the amount of diagnostic tests, but only if these tests are less of a financial burden than therapy. The idea behind this is that more diagnostic tests would eventually lead to earlier detection of disorders and therefore the costs of therapy could decrease since the focus would change to a preventive type of therapy instead of the expensive complete therapy. In 2011 there was a lobby in favor of improving the implementation of new diagnostic innovations. The president of the IFCC congress stated that the inclusion of innovations lagged in several areas of diseases dramatically behind medical progress and that this should be improved. The results of clinical research should reach the patients faster. In 2011 there was a lobby against the use of PoC devices by a director of a German private laboratory. It was stated the PoC devices show too many errors and are therefore not able to replace (a part of) the laboratory tests.

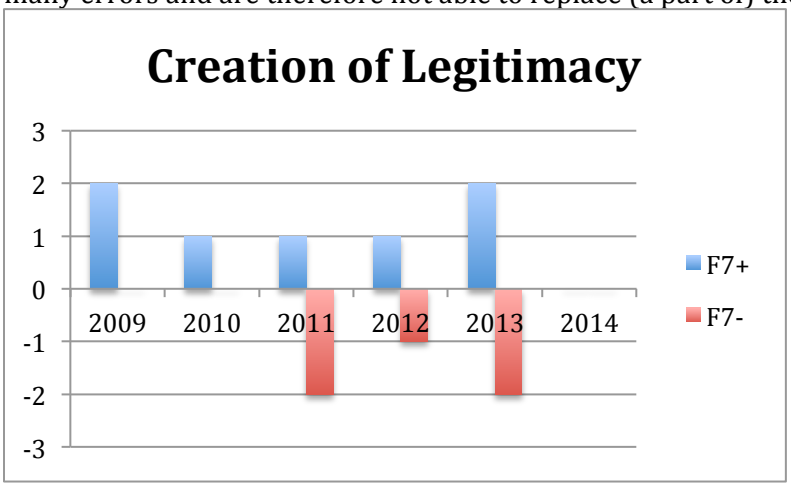

Figure 21. Function 7. Creation of legitimacy in Germany

2012-2014

In 2012 there was a lobby in order to make the laboratory market a rational market. With this is meant that the focus should be on the patient and his wellbeing. The laboratories should be

able to give the answer to particular diagnostic questions, but with a high level of security. The result of the analysis should lead to clear and effective diagnostic or therapeutic consequences. The laboratory market should become demand-driven instead of supply driven. This seems to be in some conflict with the lobby of the German government in 2010 to increase diagnostic tests if they are less expensive than the therapy. But a demand driven market also focuses on the direct transportation and analysis of (emergency) diagnostic samples/tests. In 2013 the president of the DGKL lobbied in favor of the use of own laboratories by the hospitals in Germany. These laboratories are not only used for tests but also for educating and training new specialists and other laboratory personnel. A professor in Germany lobbied against the outsourcing of laboratory activities by university (medical centers), because this will have a negative effect in the long run (scientifically and economically). A negative effect is foreseen because the collaboration between physicians and scientists to research new diagnostic methods is seen as a bridge between basic research and clinical practice and therefore makes it possible for new methods and products to become successful. This could therefore be affected by the outsourcing activities. Also, the laboratory physicians are increasingly dependent on the research and education in this field. The training of (new) specialists could be affected negatively. In 2013, Sonic got an approval for the acquisition of a laboratory. This shows that the German government/legislative bodies are not unwilling to a situation in which large laboratories could achieve economies of scale through both the implementation of the newest technologies and by increasing the volume of tests.

In Germany there were some concerns about the role of the GP. It was stated by an English reporter that doctor hopping is a true problem in Germany. Since the GP does not have a gatekeeper role, doctor hopping occurs. German patients hop from one doctor or specialist to another in order to maximize their health care possibilities and there is no actor to coordinate the patients. This leads to higher costs of health care for Germany. The author stated that Germany is therefore looking for a different model in which the role of the GP becomes more like a gatekeeper.

The function "Creation of legitimacy" shows that in Germany there are no barriers identified that could have a negative impact on the consolidation process of the medical laboratories. The data has shown that the lobbies are concerned with improving the innovative character of the primary diagnostic system. There was a lobby in favor of an improved implementation process for new diagnostic technologies. But it is also shown that there are too many unnecessary diagnostic tests performed in Germany. Although this could lead to lower costs of treatment, several lobbies were against this overuse of diagnostics.

Performance

Germany

In table 4 the indicators for performance have been shown in the upper column. The Total Healthcare Expenditures (THE) are shown in millions (Euro), together with the In-Vitro Diagnostic Market expenditures (IVD mkt.). Also the percentage of the in-vitro diagnostic expenditures of the total healthcare expenditures is shown.

The data show that the THE have increased between 2009 and 2011, but decreased in 2012 with 0,48%. The expenditures on IVD showed a different pattern. After 2009 the expenditures on the IVD market showed a small decrease of 0.55%, but in 2011 these expenditures increased with 2.55% to a total of 2 212 million Euros. Thereafter there was again a decrease of the expenditures on the in-vitro diagnostic market. The expenditures on the IVD market per capita show the same results, although hardly any changes occurred in 2011.

Also the percentage of expenditures on the in-vitro diagnostic market of the total health care costs decreased over the years. In 2009 this was 0.82%, but in four years this has decreased to 0.76%. Especially the decrease in 2012 is noteworthy, because in that year also the total health care expenditures decreased. So the expenditures on the in-vitro diagnostic market had to decrease more than the total health care expenditures.

Table 4. Performance in Germany

Germany	THE (mil Euro)	% Increase	IVD mkt. (mil Euro)	% Increase	IVD mkt/THE	IVD mkt/Capita (Euro)	Source
2009	263216	4,14%	2169	2,94%	0,82%	26,2	EDMA, 2009
2010	278345	5,75%	2157	-0,55%	0,77%	26,1	EDMA, 2010
2011	288177	3,53%	2212	2,55%	0,77%	27,1	EDMA, 2011
2012	286787	-0,48%	2169	-1,94%	0,76%	26,1	EDMA, 2012
2013	-	-	-	-	-		
2014	-	-	-	-	-		

5. Analysis of Results

This chapter analyzes the Dutch and German in-vitro diagnostic innovation systems. When looking at the development of both innovation systems over time, several trends can be identified. These trends illustrate interdependencies between the different functions/key processes of the TIS over the period 2009-2014. This research has shown that the PoC and data exchange technologies are the most emergent technologies with regard to in-vitro diagnostic technology, because both technologies are not yet fully developed and implemented in the primary diagnostic system in both the Netherlands and Germany. So the developments of these emergent technologies per country are shown specifically in this chapter. By displaying the development of these technologies, possible barriers in the implementation process of these technologies can be identified. In this chapter first the Dutch analysis will be shown, and the development of the emergent technologies in the Netherlands will be illustrated. Second, the German analysis will be shown, and the development of the emergent technologies in Germany will be illustrated. By analyzing the results of both TIS approaches for both countries, an answer has been given to the sub question *What are possible barriers for the development and diffusion of in-vitro diagnostics technology in the Netherlands, compared to the German primary diagnostic system, over time and why?*

5.1 Analyzing the Dutch in-vitro diagnostic innovation system

The results of the TIS study of the Dutch in-vitro diagnostic system are summarized in table 5. Below the analysis of these results is shown for the Netherlands.

Table 5. TIS study in the Netherlands

System Functions	2009-2011	2012-2014
F1: Entrepreneurial activities	-Mainly Dutch small companies and university spin-offs, such as Ostendum and Pathofinder, developed new products -EPD has been canceled in 2011	-New projects started concerning the EPD in hospitals like the Jeroen Bosch Ziekenhuis -Agreement by health care providers, insurers and patients on the EPD -Project started at diagnostic center to prevent unnecessary diagnostic tests
F2 Knowledge development	-Research projects focused on clinical chemistry and medical microbiology -Too many differences between diagnostic requests -Quality of PoC devices is too low according to physicians and scientists	-Research projects focused on clinical chemistry and medical microbiology -Quality of POC devices should be proven according to a scientist
F3: Knowledge diffusion	-Partnerships between laboratories, hospitals and manufacturers -There is an abundance of 'prikposten' and the transparency of the costs of laboratories is too low	-Partnerships between laboratories, hospitals and manufacturers -Partnerships between GPs and hospitals, using PoC technology, in order to improve data exchange -Partnerships (Mergers) between SHL-Groep and Diagnostiek voor U, and other GP laboratories are canceled -Possible negative influence of the ACM on collaboration
F4: Guidance of the search	-Standard setting for clinical chemistry and medical microbiology conditions -Negative promise on the use of EPD and a lack of standards for the EPD	-Standard setting for clinical chemistry and medical microbiology conditions -Several studies show negative

	-Quality of self-tests is too low -Several studies show negative outcomes for the PoC devices (quality) -The PCA3-test shows that the reimbursement system is a barrier for the introduction of new diagnostic tests	outcomes for the PoC devices and the data exchange technology (quality) -CE marks granted for new in-vitro diagnostic product -Reimbursement system is a barrier for new self-tests -The health insurance companies have too much power -Positive promise that consolidation of laboratories will lead to efficiency
F5: Market formation	-Hospitals take over a part of the primary diagnostic market -St. Elisabeth hospital invests in new laboratory -Niche market for EPD at the hospitals -PoC technology will be unable to take over the laboratory	-Niche market for PoC at the GP practice -Mediator prevents unnecessary diagnostic test
F6: Resource mobilization	-The Dutch government invests 125 million Euro in the application of micro- and nanotechnology in diagnostics -Shortage of medical microbiology specialists -Boercroon expects the increase of private equity	-Mergers between laboratories in Friesland and Groningen and merger of laboratories into Certe -Subsidies by the EU to develop certain products -Reimbursements system of PoC devices shows flaws
F7: Creation of legitimacy	-Lobby by scientific association against the use of PoC devices -NZa released their advice on how to improve the primary diagnostic system; financial report by Plexus -Both the Dutch government and organizations such as Boercroon lobbied to improve the primary diagnostic system -Hospitals should abandon their primary diagnostic activities	-Several guidelines are released by the NZa to improve the primary diagnostic system -Consolidation is lobbied for by the Dutch health insurance company VGZ -ACM allowed the merger of laboratories into Certe -Lobby by a medical specialist to further implement the EPD
Performance	-Increase of expenditures on the IVD market till 2011	-Decrease of expenditures on the IVD market in 2012

2009-2011

In the period between 2009 and 2011 there seemed to be a lack of resource mobilization [F6]. Hardly any data shows the availability of capital invested in the primary diagnostic innovation system in the Netherlands and the investments that have been made, were made by the manufacturers or the Dutch and European government (Subsidies). The purpose of these investments was to further develop and implement the in-vitro diagnostic technology in the Netherlands. The amount of projects started and products introduced [F1] have increased over time in this period and were mainly initialized by smaller Dutch and international companies, such as Biocartis and Pathofinder, and university hospitals. Only Biocartis has been identified as a rather large company that has started new entrepreneurial projects. In this period both fundamental and applied research has been conducted [F2], by mainly Dutch scientists and medical specialists, but the amount of new research projects has slightly decreased after 2009.

In the period between 2009 and 2011, many Dutch GP laboratories and Dutch hospital laboratories started to collaborate with each other in order to improve knowledge diffusion, to increase the economies of scale and become more viable as an organization [F3]. This has led to larger diagnostic laboratories, in terms of space and units of diagnostic tests, and more efficient diagnostic laboratories. This period also describes the implementation of fully automated

laboratory systems, which have found their niche market in these new larger laboratories [F5]. For both periods (2009-2011 and 2012-2014) only mergers and partnerships have been identified for the GP and hospital laboratories. The interviews have shown that due to the legal forms of these laboratories, founded as mainly foundations, take-overs are not possible. This could be an explanation for the lack of capital investments and resources in Dutch laboratories [F6]. One of the goals of the mergers and collaborations is to operate more efficiently. The use of 'prikposten', for example, is seen as inefficient. Both the data and interviews have shown that the use of these 'prikposten' in the Netherlands leads to higher personnel costs for example.

The Dutch government (Ministry of Health, Welfare and Sport) and the NZa lobbied in 2011 in favor of the shift from primary diagnostic activities in the second line (hospitals) to the first line (GP laboratories and GPs) [F7]. Between 2009 and 2011, however, still many hospitals laboratories merged, and the St. Elisabeth Hospital implemented a complete new automated diagnostic laboratory in order to analyze more diagnostic samples [F5]. So although there is the recognition by the government, the problem has still not yet been solved. This is confirmed by the hospitals that still take over parts of the primary diagnostic market from the GP laboratories [F5].

There was an increase of the expenditures on the in-vitro diagnostic market [Performance], which led to the advice reported by the NZa to the Dutch government on how to improve the Dutch primary diagnostic system [F7]. Also lobbies have been made in favor of the improvement of the innovation process in the primary diagnostic system by, for example, the consultancy company Boercroon [F7]. Innovation in the health care in the Netherlands was affected by a lack of focus on technological developments by policy makers. After these lobbies, that have been made in order to indicate the importance of technological development in the primary diagnostic system, several focused on different in-vitro diagnostic technologies (for example, data exchange) have been started [F1]. But standards are still lacking for the new innovations to become implemented in the reimbursement system [F4]. There are still flaws in this reimbursement system, which leads to delayed implementations of innovations.

2012-2014

In 2011, the NZa released their advice and consultation about possible improvements of the primary diagnostic system in the Netherlands [F7]. Thereafter, as described in the textbox "2015: A new way of funding the GP labs", the primary diagnostic system did change. The consolidation process has continued in the Netherlands. Laboratories, both for GPs and hospital, engaged in partnerships or (physically) merged with each other. A Dutch health insurance company (VGZ) lobbied in favor of this consolidation process [F7]. Also the reimbursement system changed. The reimbursement system for both the hospital laboratories and GP laboratories is now equal; therefore no party can earn more by their primary diagnostic activities [F6]. However, standards lack in the reimbursement system, which leads to innovations (new diagnostic devices and tests) that are not included sufficiently and within a short time span in the reimbursement system [F4]. So standard setting is still lacking for the implementation of new products in the reimbursement system. The NZa has released several guidelines after 2011 in order to change and improve the primary diagnostic system [F7]. It was even stated that many unnecessary diagnostic tests have been prevented by a Dutch medical center (Medisch Coördinerend Centrum Omnes) [F5]. This may also have led to a decrease of the expenditures on the Dutch in-vitro diagnostic market after 2011 [Performance].

In the period between 2012 and 2014 several lobbies by Dutch high tech start-ups and Dutch scientists have been made in favor of technological development in the primary diagnostic

system [F7]. The health insurance companies are in charge of the health procurement and could thereby differentiate between different types of tests or diagnostic devices. But the health care insurance companies are perceived, by a director of the Dutch health insurance company DSW, as having too much power [F4].

The consolidation process of the laboratories has continued in the period between 2012 and 2014. Regulatory approval by the ACM has led to the merger between several GP laboratories into the Certe laboratory [F7]. But the ACM could also hinder mergers and knowledge diffusion when it overregulates the primary diagnostic system, focused on mergers and partnerships between laboratories [F3].

The Netherlands; The emergent technologies[12]

The Point of Care technology and Data exchange technologies have shown to be emergent technologies in this research, because these technologies are not yet fully implemented. In order to show any barriers in the implementation process, a focus has been made on these two technologies. In figure 22 and figure 23 the results of all functions/key processes have been illustrated for both emerging in-vitro diagnostic technologies in the period between 2009 and 2014.

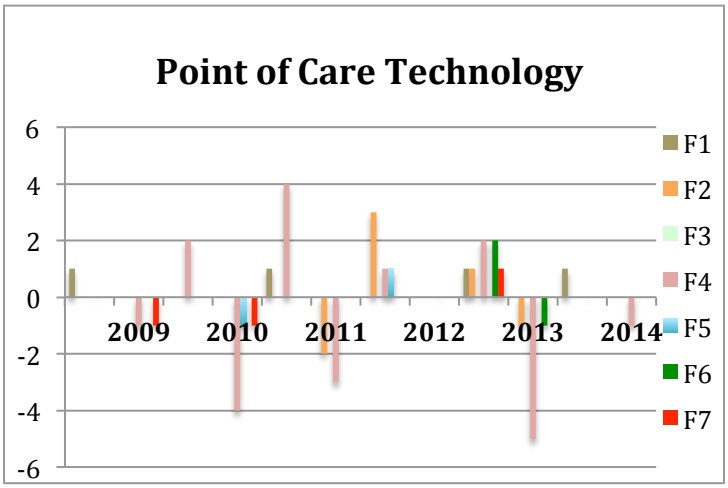

Figure 23. Analysis of the PoC technology

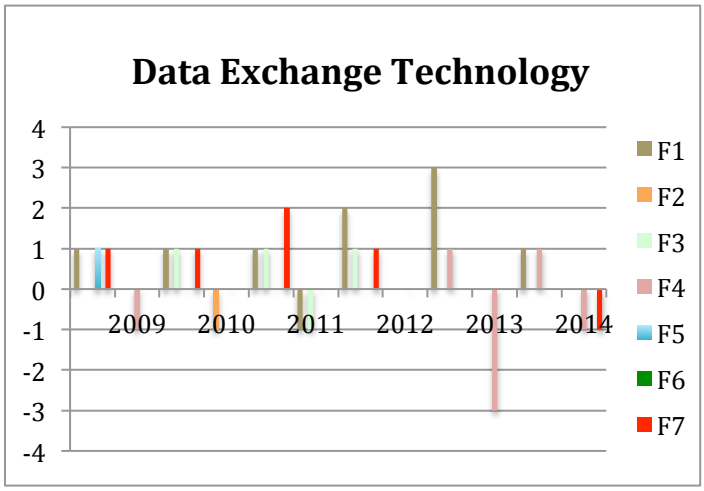

Figure 22. Analysis of the Data Exchange technology

The TIS analysis has shown that the amount of scientific articles and patents applied for (worldwide) shows an increase over time [F2]. But no data has been found on whether or not this knowledge that has been developed has been diffused among the actors in the primary diagnostic system [F3]. Therefore also no direct influence on the amount of new projects or products has been identified. The PoC technology shows, however, that several entrepreneurial activities took place in the Netherlands over the period between 2009 and 2014 [F1]. These entrepreneurial activities, however, do not show a clear increase or decrease over time. The studies conducted assessing the quality of the PoC technology have shown that still many improvements need to be made, since the current PoC devices still show too many flaws [F4]. Lobbies against the use of PoC technology have been carried out by the NVMM (scientific association) and the RIVM due to these flaws [F7]. Complementary, market formation [F5] has shown that the PoC technology will not take over the complete laboratory market. However, in

[12] The patent and scientific article analyses (Knowledge development; [F2]) have not been illustrated in these figures, because only country specific results are shown.

the following years a niche market at the GPs practices has been identified for the PoC technology [F5], investments have been made in order to develop and implement the technology [F6] and lobbies in favor of the use of PoC technology took place [F7]. The reimbursement system for PoC technology however is still not in place [F6]. The lack of entrepreneurial activities could be the outcome of the relationships of the diagnostic manufacturers with the (GP) laboratories. The manufacturers act as strategic partners for these laboratories and could thereby have developed a business model focused purely on these laboratories and sales to these laboratories. This path dependency could focus the manufacturers away from the further development of PoC devices and implementation at GP practices.

The emerging data exchange technology, like IT systems such as the EPD, in the Netherlands, has shown that several Dutch agencies (NVZ/IGZ) and medical specialists have lobbied in favor of the use of data exchange technologies in the primary diagnostic system [F7]. Also the amount of products and projects has slightly increased over the years [F1], and the data exchange technologies has been used to exchange data between different actors in the primary diagnostic system [F3]. But negative test results, mainly regarding privacy and safety of the data exchange technology (EPD in specific), have been identified over the complete period between 2009 and 2014 [F4]. Also the amount of different IT systems for the exchange of data between actors in the primary diagnostic has made it difficult to set standards and implement this technology [F4].

5.2 Analyzing the German in-vitro diagnostic innovation system

The results of the TIS study of the German in-vitro diagnostic system are summarized in table 6. Below the analysis of these results is shown for Germany.

Table 6. TIS study in Germany

System functions	2009-2011	2012-2014
F1: Entrepreneurial activities	-Many new projects through partnerships between laboratories, manufacturers and institutions -Large companies such as Roche and Abbott launched new products -Many projects focused on the development of PoC technology and data exchange technology	-Large companies such as Roche launched new products -Several projects focused on the development of PoC technology and data exchange technology -Research institutes, such as the Fraunhofer institute, developed new projects
F2: Knowledge development	-Research mainly focused on clinical chemistry and medical microbiology	-Research mainly focused on clinical chemistry and medical microbiology The health insurance company as a source for data on the market
F3: Knowledge diffusion	-Many partnerships between laboratories and manufacturers to develop new products -Medica and IFCC conferences -Siemens showcase on their new products	-Shift from conferences, such as Medica, to scientific conferences such as IFCC-Worldlab -Seminar by the German Society for Biomedical Engineering on PoC testing -International partnerships to develop new products, for instance Siemens Healthcare and Pfizer
F4: Guidance of the search	-DIN EN ISO 15189 standard introduction -Assessment studies on PoC devices show negative outcomes; but positive expectations about the future of the PoC technology -The MALDI Biotyper-Workflow receives CE-	-Personnel has to be trained to work with PoC devices -CE-mark for PoC device and other in-vitro diagnostic device -Positive expectation by medical

	marking The quality of diagnostic tests in Germany increased	specialist on the future of PoC -Standards are introduced for the use of Microarrays (applicable in PoC)
F5: Market formation	-Niche markets for PoC in emergency diagnostics and hospitals; but not able to take over the in-vitro diagnostic market -Niche market for data exchange technology in medical laboratories and PoC testing -There are too many IT systems in the German primary diagnostic market -Private insured citizens receive far more tests than statutory insure citizens -Too high amount of unnecessary diagnostic tests	-Niche market for data exchange technology in laboratories and hospitals. -Niche market for PoC technology in hospitals -Distortion between private and statutory insured markets -A distortion in the market for private and compulsory insured citizens -Private insured citizens receive far more tests than statutory insure citizens
F6: Resource mobilization	-Consolidation process of German laboratories -German laboratories are acquired by international companies such as Sonic Healthcare -German reimbursement system does not obtain new in-vitro diagnostic products sufficiently -Hospitals outsource their diagnostic tests because it is too expensive	-Consolidation process of German laboratories -Sonic Healthcare buys Labco -There is a lack of labor specialists -Investments made by Bonn University to improve research towards in-vitro diagnostic technology -Roche invests 200 million Euro in new Diagnostic research complex
F7: Creation of legitimacy	-Sonic Healthcare gets the approval of the German government to take over German laboratories -Lobby by the director of the Institute for Quality and Efficiency in Health Care to decrease the over diagnosing of private insured citizens -Governmental lobby for more diagnostic tests -Lobby against the use of PoC technology by a laboratory specialist	-Doctor hopping in German healthcare system -Lobby by the director of DGKL against the outsourcing of diagnostic activities by hospitals -Lobby by professors against the amount of (unnecessary) diagnostic tests; in favor of buyer market
Performance	-Decrease of expenditures on the IVD market in 2010 -Increase of expenditures on the IVD market in 2011	-Decrease of expenditures on the IVD market in 2012

2009-2011

Between 2009 and 2011 there was an increase of knowledge diffusion [F3]. Many partnerships between German diagnostic manufacturers, but also laboratories and other types of organizations such as research institutes (Rober-Koch-Institut for example) took place in this period to develop new diagnostic (related) products. In this period also the entrepreneurial activities [F1] increased. Many of these collaborations led to the introduction of new in vitro diagnostic products. Also products to improve the data exchange between actors in the primary diagnostic system in Germany have been developed. Often these products were shown at conference like Medica in order to diffuse the knowledge on the new in-vitro diagnostic products [F3]. In 2009, Resource mobilization [F6] showed a peak. Several investments, for example by private equity companies such as BC partners, were made in Germany in order to stimulate the development of new diagnostic products. Again, there was an increase of entrepreneurial activities after 2009 [F1].

Many of the investments made, were take-overs of laboratories by international companies such as Sonic Healthcare. This was approved by the German regulation [F7], which allowed these types of take-overs by large international companies. Next to the regulation, also the legal forms of the laboratories allowed the take-overs to be possible. The laboratories are companies under stock exchange, which make it possible to be taken over hostilely. As the interviews and

German NIS have shown, the German laboratories operated extremely efficient, which also made these organizations interesting for the large international companies such as Sonic Healthcare. This in combination with the regulations, made sure that the consolidation process of diagnostic laboratories in Germany could take place, also shown by the many investments and acquisitions [F6] made by laboratories and other organizations in Germany.

In 2009 it was stated by a professor in Germany that there were too many unnecessary tests conducted in the medical clinics in Germany [F5]. In 2010, the problem of the distortion between private and statutory insured people was shown [F5]. The diagnostic market for private insured people is much larger than for the statutory insured people. This is seen as a major concern because many of these tests are unnecessary and thereby increasing the costs of the primary diagnostic market. The German government, however, lobbied in favor of more diagnostics, but only if this will lead to lower costs by preventing further therapy [F7]. So although the primary diagnostic market shows several flaws, lobbies, by inter alia the government, were focused to reduce the costs of the primary diagnostic system. This has positively stimulated the performance in Germany [Performance]. The expenditures on the primary diagnostic market have increased with 2.55% after 2010.

In 2011, the shortcomings of the German reimbursement system [F6] were illustrated by a spokesman of the Verband der Diagnostica-Industrie e.V. (VDGH). This system was not able to adopt new in-vitro diagnostic innovations, new products, rapidly enough. The implementation of new devices in the primary diagnostic system has also been lobbied for by the president of the IFCC congress [F7]. In the same year several new products were introduced and projects were started [F1]. Also, as already stated above, several (niche) markets for PoC have been formed in that period [F5]. This shows that the flaws in the reimbursement system didn't seem to affect other key processes in German in-vitro diagnostic developments in the period between 2009 and 2011.

2012-2014
The flaws in the German reimbursement system [F6] did not seem to lead to any decreases in product introduction and projects started in 2011 [F1], but in 2012 the amount of German in-vitro diagnostic projects and products decreased [F1]. Market formation [F5] showed a decrease of new (niche) markets for, inter alia, PoC products.
Although the amount of new products introduced and projects started decreased [F1], more and more knowledge on in-vitro diagnostic technologies has been diffused [F3]. The interviews and data have shown that there was a shift in the type of knowledge diffusion. This shift refers to the former situation of conferences where only products were shown, like Medica, to scientific conferences where the products are also validated scientifically. The scientific article analysis and the other studies show that there is an increase of research conducted over the years [F2].

More and more German hospitals began with outsourcing their diagnostic activities to other (private) laboratories [F6]. The market for the in-vitro diagnostic technologies decreased hereby, but it also hampered the education and training of laboratory specialists [F7]. Outsourcing of diagnostic tests also has a negative influence on the turn-around time of the diagnostic tests. (University) hospitals should therefore not abandon their laboratories, according to the president of the Deutschen Vereinten Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V (DGKL; German society for clinical chemistry and laboratory medicine).

It was stated by an English reporter that 'doctor hopping' is a true problem in Germany and that Germany is looking to a different model. In this model, the GP should be granted a role like a gatekeeper in order to reduce the volume of the (unnecessary) diagnostic tests [F7]. So this problem in the German healthcare system has not been solved over the years, but does not seem to have affected other functions or the performance of the in-vitro diagnostic technology. The costs of the primary diagnostic market even lowered after 2011, as is shown by the expenditures on the in-vitro diagnostic market [Performance]. However, a lack of human capital [F6], such as laboratory specialists, occurred, even though in 2010 a partnership [F3] between Abbott Diagnostics and DGKL was introduced, focused on improving this lack of human capital.

Germany: The emergent technologies[13]

Also for Germany, a focus has been made on the emergent technologies (PoC and data exchange technology) in order to identify any barriers in the implementation process. In figure 24 and figure 25 the results have been illustrated for both technologies in the period between 2009 and 2014.

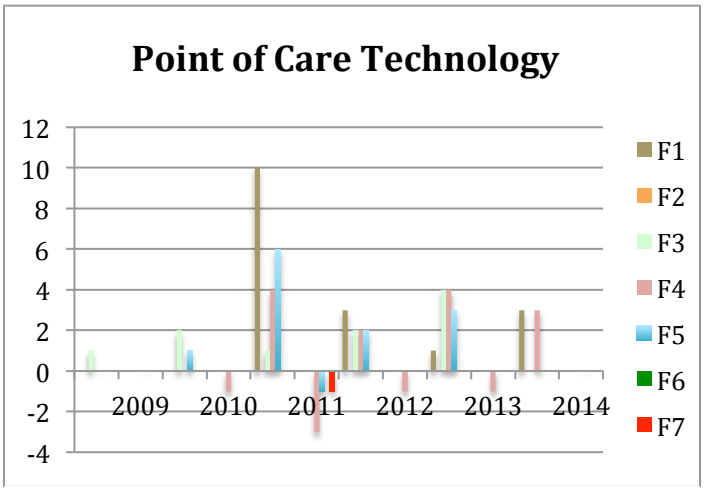

Figure 25. Analysis of the PoC technology in Germany

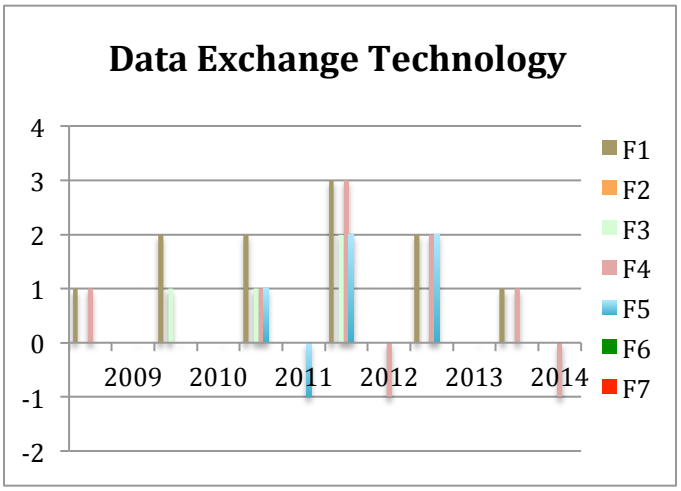

Figure 24. Analysis of the Data exchange technology in Germany

The TIS analysis showed that both the scientific articles and patents focused on PoC increased in this period [F2], and figure 24 shows that knowledge also has been diffused [F3]. But in 2010 and 2011 more and more negative scientific outcomes of studies [F4] were published, as well as lobbies by a manager at a private laboratory against the use of PoC devices [F7]. This does not seem to influence the other functions because in 2011 more PoC products were introduced by large companies (Siemens), universities and research institutes (Fraunhofer Institute) [F1], and more (niche) markets were formed [F5]. After 2011, the amount of negative outcomes of studies decreased [F4], while activities concerning market formation [F5], knowledge diffusion [F3] and entrepreneurial activities [F1] remained. New products are still being developed, and the PoC technology appears to have found niche markets in hospital departments and emergency diagnostics in Germany.

[13] The patent and scientific article analyses (Knowledge development; [F2]) have not been illustrated in these figures, because only country specific results are shown.

The data exchange technology, for example IT systems, shows that in the beginning of the period 2009 and 2010 in Germany mainly products were developed/introduced [F1] and knowledge was diffused [F3]. This has led to market formation [F5] in 2011, but also to an abundance of IT systems. After 2011, new markets have been formed, such as the use of IT systems in laboratories [F5], new products, such as the management of laboratories in the cloud and e-government services, have been introduced [F1] and knowledge on the use of data exchange products has been diffused [F3]. Especially laboratories make more use of data exchange systems. Several systems are used to connect systems with each other, but systems are also used to connect departments or organizations with one another. However, in 2014 doubt and uncertainty have been expressed by a representative of a medical legal firm about the privacy and confidentiality of the use of data exchange technologies such as IT systems in the German primary diagnostic system.

6. Conclusion

This research has focused on the problem of the increasing healthcare costs in the Netherlands in relation to the Dutch primary diagnostic system. In the Dutch primary diagnostic system, several bottlenecks resulted from the intertwinement of the primary diagnostic system with the (more expensive) second line diagnostic system. These bottlenecks increased the costs of the primary diagnostic system and thereby the healthcare costs in general in the Netherlands. The Dutch primary diagnostic system should therefore be improved, as acknowledged by the Dutch government and other Dutch institutions. The German primary diagnostic system is perceived as one of the most efficient primary diagnostic systems. Especially the German laboratories operate more efficient than the Dutch laboratories, resulting in lower costs per diagnostic test in Germany. Therefore in order to identify the strengths and weaknesses of the Dutch primary diagnostic innovation system, a comparison with the German primary diagnostic innovation system has been made. By describing and analyzing both innovation systems, from a national and technological perspective, policy recommendations have been made that focused on improving the Dutch primary diagnostic innovation system. The in-vitro diagnostic technology[14] is central in the technological perspective. This chapter provides the answer to the research question:

What are the strengths and weaknesses of the emerging primary diagnostic innovation system in the Netherlands, focusing on the 'in-vitro diagnostic' technology, compared to Germany over the period 2009-2014?

At first, the primary diagnostic innovation systems of the Netherlands and Germany have been analyzed in order to identify and describe the main actors, institutions and their interdependencies of these National Innovation Systems (NIS). Thereafter the Technological Innovation System (TIS) approach has been applied in order to analyze the dynamics of the in-vitro diagnostic technology developments over time and to identify possible barriers in the implementation process of this technology in both the Netherlands and Germany. The TIS approach describes seven system functions/key processes. These system functions do not operate solely, but interact with each other. The in-vitro diagnostic technology will perform better if these system functions are better fulfilled. The performance of the primary diagnostic innovation system refers to the expenditures on the primary diagnostic market in the Netherlands and Germany. Analyzing and comparing both the technological innovation system of the in-vitro diagnostic technology in the Netherlands and in Germany led to an answer to the research question.

6.1 The strengths and weaknesses of the Dutch primary diagnostic innovation system

In the period between 2009 and 2014 there has been a lack of resource mobilization [F6-] in the Dutch primary diagnostic innovation system compared to the German primary diagnostic innovation system. In order to operate more efficient and gain economies of scale, the laboratories will have to merge, for example through fusions or take-overs. Due to the business models and legal forms of German laboratories, the German private laboratories were of interest and able to become acquired by large international companies such as Sonic Healthcare [F6+]. As the interviews have shown, these international companies made the German

[14] In vitro diagnostics refer to laboratory tests concerning clinical chemistry, as well as medical microbiology, 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013).

laboratories even more efficient after the take-overs. In the Netherlands, no investments by large international companies into Dutch laboratories took place. This hampered the consolidation process of laboratories in the Netherlands of which it is expected to improve efficiency in the diagnostic process. Mergers/partnerships between Dutch laboratories did take place between 2009 and 2014. Another (possible) barrier, however, is the Dutch competition regulator (ACM) that has a (possible) negative influence the consolidation process by formally rejecting possible mergers between Dutch GP laboratories [F7-].

Knowledge development in the field of the in-vitro diagnostic technology has increased for both the Netherlands and Germany in the period between 2009 and 2014 [F2+]. Knowledge diffusion has also increased over the years in the Netherlands [F3+], but there seems to be a gap between the development of knowledge in the field of the in-vitro diagnostic technology and the application of this knowledge in the Netherlands. The entrepreneurial activities in the field of the in-vitro diagnostic technology are scarce in the Netherlands, compared to Germany [F1-]. However, the entrepreneurial activities that have been identified in the Netherlands show that different kinds of in-vitro diagnostic technologies are developed or implemented, and both universities/hospitals and smaller companies are engaged in these processes. Large companies, however, do not seem to be engaged in entrepreneurial diagnostic activities in the Netherlands. One of the reasons could be that the subsidiaries of these international companies in the Netherlands are mainly focused on marketing and sales. Also hardly any of the large international in-vitro diagnostic manufacturers reported entrepreneurial activities focused on the PoC technology in the Netherlands [F1-]. The interviews showed that the manufacturers act as strategic partners for the laboratories in the Netherlands. Since PoC devices are not used in these laboratories, the focus of the large manufacturers could be on conventional in-vitro diagnostic technologies, such as clinical chemistry and automation processes.

In Germany, the PoC technology has been implemented in different niche markets, namely the emergency diagnostic market and the hospital departments [F5+]. Market formation in the Netherlands for the PoC technology hardly took place between 2009 and 2014. It was even expected that the PoC technology will not take over the current Dutch diagnostic market. So there seems to be a lack of market formation for the PoC technology in the Netherlands [F5-]. Possible influencing factors are the negative assessment studies on the quality of PoC devices and the negative opinions by scientists and other stakeholders in the Dutch primary diagnostic system [F2-/F4-]. These negative studies and opinions on the PoC technology led to lobbies against the use of the PoC technology in the Netherlands [F7-]. This research has shown that also an appropriate reimbursement system is lacking for the use of PoC devices in the Netherlands [F6-]. This shows that guidance of the search [F4] and knowledge development [F2] influenced creation of legitimacy [F7] negatively. This led to the absence of market formation [F5] and resource mobilization [F6].

Lobbies by several government institutions and experts have advocated in favor of the use of IT systems like the EPD and an improvement data exchange in the primary diagnostic system in the Netherlands [F7+]. Also several projects were started concerning data exchange technologies in the Netherlands [F1+]. The data exchange technology, however, has shown several negative outcomes of studies on the assessment of this technology [F4-]. There is an abundance of IT systems available for the actors in the primary diagnostic system in the Netherlands [F4-], which makes it more difficult to set standards for these data exchange technologies [F4-]. Also the safety and privacy of the data of patients in these IT systems has been questioned [F4-].

One of the problems of the Dutch primary diagnostic system is the intertwinement of the first line (primary diagnostic system) with the second line diagnostic care. This research has shown that hospitals in the Netherlands invest in their laboratories [F5+/F6+], but also take over parts of the primary diagnostic market [F5-]. As is shown in reports by the NZa (Conquaestor, 2011) and Plexus (2010), this leads to higher costs of the primary diagnostic system [Performance-]. In Germany the hospitals are increasingly outsourcing their primary diagnostic activities [F5-]. Although this is experienced as negative for the development of the in-vitro diagnostic technology and human capital (training of personnel), it shows that there is less intertwining of diagnostic systems in Germany. The German hospitals are, however, smaller than the Dutch hospitals, which makes it unaffordable for the (smaller) German hospitals to retain their laboratories and laboratory activities.

The amount of unnecessary diagnostic tests in Germany is too high [F5-]. The distinction in the German health care system between private and statutory insured people has also led to a distortion and abundance of the amount of (unnecessary) diagnostic test [F5-]. Furthermore, lobbies have shown that there is no gatekeeper role for the General practitioner (GP) in Germany, which leads to so called doctor hopping [F7-]. This also leads to an abundance of unnecessary diagnostic tests in Germany. In the Netherlands, the GPs have a gatekeeper role and could therefore coordinate the patients, withhold them from doctor hopping and reduce the costs of health care.

The involved role of the government and governmental institutions in the Netherlands has led to a decrease of the expenditures on the in-vitro diagnostic market [Performance+]. In 2011, the Nederlandse Zorgautoriteit (NZa) released their advice on how to improve the Dutch primary diagnostic system [F7+], and in 2012 the expenditures on the in-vitro diagnostic market decreased with 3.13%. The NZa has released several other stimulating guidelines in the years after 2011, accompanied by several lobbies from the government, a consultancy company and researchers to change the primary diagnostic system in the same period [F7+]. The consolidation process has continued thereafter [F6+/F3+], leaving the probability that the laboratories are operating more efficient and thereby decreasing costs of the primary diagnostic system. The amount of unnecessary diagnostic tests has decreased after the actions by the Dutch governmental/supervisory institutions [F5+]. Also several projects were started in order to decrease the amount of unnecessary diagnostic tests in the Netherlands [F1+]. So the creation of legitimacy [F7] stimulated the entrepreneurial activities [F1], knowledge diffusion [F3], market formation [F5] and resource mobilization [F6], which lead to a decrease of the expenditures on the in-vitro diagnostic market [Performance]. The creation of legitimacy [F7] was initially stimulated by the high expenditures of the in-vitro/primary diagnostic market [Performance-]. The acceleration of the TIS through the creation of legitimacy [F7] indicates that there is a motor of innovation, although no persistent feedback loop has been identified. This is illustrated in figure 26.

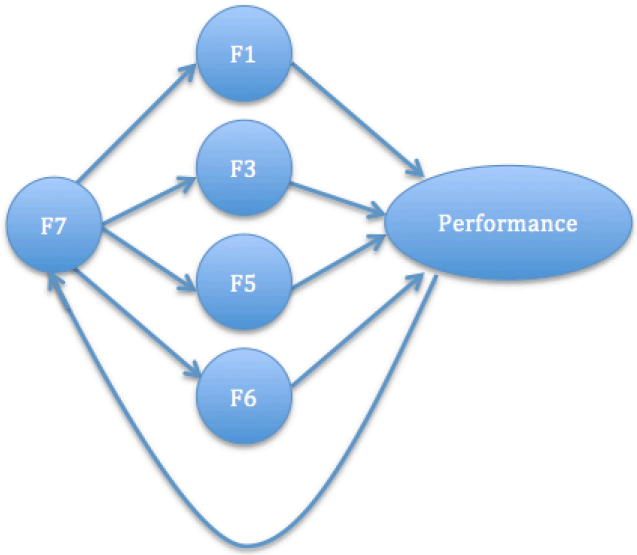

Figure 26. Motor of innovation and the influence on Performance

6.2 Policy recommendations

Creation of legitimacy [F7] has shown through the introduction of new guidelines and new policies by the NZa, that the Dutch government is already willing to improve the Dutch primary diagnostic innovation system. This research has shown that both the Dutch primary diagnostic innovation system (organizations and interdependencies) should be further improved and that barriers experienced by the emergent in-vitro diagnostic technologies should be overcome. This part will therefore give an answer to the sub question *How could these barriers be overcome?*

This research has shown that GP laboratories in the Netherlands operate less efficient than the German private laboratories. The German (private) laboratories were also founded through different legal forms and business models than the Dutch (Gp) laboratories. This led to more investments made by international companies in the German primary diagnostic system [F6]. Take-overs by large international companies led to more efficient operating processes of the private laboratories in Germany. The operating processes of the Dutch laboratories are less efficient than the German laboratories. The Dutch government should provide the Dutch laboratories with incentives and opportunities to operate more efficient. So the Dutch competition regulator (ACM) should not restrict the partnerships and mergers of laboratories in the Netherlands too fiercely [F7]. The Dutch laboratories could also learn from the business models of the German private laboratories. In Germany, the diagnostic samples are taken at the GP's office, collected by courier services and brought to the laboratories. In the Netherlands, the laboratories make use of so-called 'prikposten'; from wich the samples are send to the laboratory. This leads to higher costs of personnel and a delay for the patient because he/she has to visit this 'prikpost'. One project in 2014 already started by collecting all diagnostic samples at the GP and then delivering these samples to the laboratories.
This research shows that hospitals still take over parts of the primary diagnostic market, but as stated above the Dutch government and the NZa are already tackling the intertwinement of the

primary and second line diagnostic systems, for example by introducing new guidelines [F7]. After the transition model in 2014 (described in the textbox "2015: A new way of funding the GP labs"), the health insurance companies will be able to differentiate between the most efficient laboratories. This could already be a stimulans for the laboratories to operate more efficient. The Dutch government should also stimulate the development of new projects [F1]. The results show that knowledge is being developed (both globally and nationally), but the amount of new projects and products in the field of in-vitro diagnostics seems to lack behind. The shift from knowledge development to commercialization should be stimulated in the field of in-vitro diagnostics. This could be accomplished by stimulating collaboration between different actors, especially between manufacturers, laboratories and scientists. The results hardly show any partnerships between these three types of actors.
Standard setting [F4], the creation of niche markets [F5] and the reimbursement system [F6] need to be improved in order for the emerging technologies, PoC technology and data exchange technology, to become successfully implemented. For the PoC technology also further research [F2] is important, since many studies showed negative results for the quality of these devices and the use thereof. For the data exchange technology, standard setting is important, since there are many different systems, different actors and different manufacturers. But also niche markets will have to be created or stimulated. The data exchange technology seems to have found several niche markets, but for the PoC technology there is mainly the GP's office as its niche market. When looking at Germany, also emergency diagnostics and hospitals departments could be a more promising market. At last the reimbursement system should be structured in such a way that the innovation become reimbursed more quickly. This would overcome the barrier of new diagnostic devices that do not become implemented in society because of a lack of reimbursement.

7. Discussion

This research has focused on the problem of the increasing costs in the Dutch primary diagnostic system. This has been a problem for years in the Netherlands, and the Dutch government has recognized that several changes in this system have to be made. The results of this research showed however, that higher costs in the primary diagnostic system do not have to be detrimental to the overall healthcare costs in a country. More diagnostic testing could prevent further, more expensive, treatments and thereby reduce the healthcare costs. Increasing costs of diagnostics, however, are still an indicator that there could be deficiencies in the Dutch primary diagnostic innovation system. This was also the outcome of several studies by Dutch (governmental) institutions.
The choice of delineation for the Netherlands and Germany seemed to be adequate. The problem of the increasing healthcare costs is very relevant in the Netherlands and the German diagnostic processes showed to be more efficient than the Dutch diagnostic processes. The German primary diagnostic innovation system is thus perceived as a success case in this research and suitable to be compared with the Dutch primary diagnostic innovation system. Also the period for this research, 2009 to 2014, has shown to be adequate. The PoC technologies and data exchange technologies showed to be emerging technologies in this time period. At present, the technologies are not yet implemented completely. The data on the performance of these technologies however, was only available from 2009 to 2012. So no conclusion can be drawn on the performance for 2013 and 2014. Further research could obtain these data for 2013 and 2014. In this research the in-vitro diagnostic technology stood central. It turned out that this technology can be divided into clinical chemistry, medical microbiology, Point of Care and self-testing. Furthermore, the results showed that data exchange technology was also of importance for this research. Follow-up studies should be conducted to create more in-depth knowledge about these in-vitro diagnostic technologies separately, and on their interrelations.

This research has combined an analysis of the current structure of the primary diagnostics innovation systems of the Netherlands and Germany with a functional analysis of emerging in-vitro technologies in these systems. This has led to a comprehensive description of the Dutch and German primary diagnostic system, and the functional analysis led to new insights into important key processes that influence the in-vitro diagnostic technology and their interdependencies. Several interesting results have been found for the Dutch primary diagnostic system and compared with results of the German diagnostic system. Also the emergent technologies, PoC and data exchange technologies, have been studied more intensively by plotting figures of the complete period focused on only these technologies. The results have shown clear weaknesses and strengths of the Dutch primary diagnostic system, even though there is no causal relationship between the functions and the performance indicator. Further research will have to show the causal relationship between the weaknesses/strengths and the performance of the Dutch in-vitro diagnostic system. Policy recommendations have been given in this research in order to lower the barriers identified within the seven functions/key processes of the Dutch in-vitro diagnostic innovation system.

Both the National Innovation Systems (NIS) and the Technological Innovation Systems (TIS) approaches have proven to be able to adequately describe the current state of the primary diagnostic systems and to give a dynamic analysis of the technologies. Another possible theoretical approach could have been the Multilevel Perspective (MLP) theory by Geels (2002) in order to describe the transition of new technologies to the landscape. The MLP theory could show in depth how the primary diagnostic system is changing. New technologies, like the PoC

technology, are expected to develop within a niche and possibly take over the current regime (current technologies). However, in order for this to happen pressure from the (sociopolitical) landscape should occur. Several factors, such as economic pressures or social trends, influence the pressure of the (sociopolicitcal) landscape. By using the MLP approach, the transformation of the (sociopolitical) landscape could be studied in depth, focusing on this transition. This study has shown that the PoC technology is unlikely to take over the whole diagnostic market, but by using the MLP approach, the (sociopolicitcal) landscape could be studied in order to analyze these barriers more specifically.
Since the regulations and guidelines are changing rapidly in the Dutch primary diagnostic system, theory on the influence of institutions on the implementation of emerging technologies could also be insightful to study the current transition in the Dutch primary diagnostic system. Institutional theory has been described by for example Scott (2008) and Berman (2012).

This research has focused on data acquired through a desktop study, both scientific and common data, and through interviews. The interviews have also been used to verify and elaborate on the data acquired through the desktop study. A difficulty was the choice of the performance indicators. Originally the amount of PoC devices already used by hospitals and GPs, data about the costs per in-vitro diagnostic test and data on the volume of the in-vitro diagnostic tests over time were used as indicators for measuring performance in this research. However no data was available for these indicators. Therefore different data has been used; namely the expenditures in the in-vitro diagnostic market and the percentage of these expenditures of the total healthcare expenditures. But this indicator does not show, in detail, whether or not the in-vitro diagnostic system is doing "better" in terms of efficiency. The total expenditures on the in-vitro diagnostic market are a combination of both the costs per test and the volume of the total tests. So although the costs per test could decrease, if the volume increases enough the total expenditures on the in-vitro diagnostic market could still increase. This indicator does show however how well the in-vitro diagnostic market is overall performing.
The interviews showed that the interviewees, being different actors in the primary diagnostic system, sometimes contradicted each other. This, however, gave new insights from different perspectives in barriers such as the lack of information exchange between the different actors in the system. This also provided this research with underlying insights and motives in system functioning by the different actors and verification of the gathered data.
Reliability has been proven through triangulation. In the interviews the data has been verified, and a Dutch director of a GP laboratory has evaluated the German NIS. All data has been coded and stored. The method of this research has been fully described, so other researchers could perform the same research, compare the data with the current data and compare the results. However, only the country specific (scientific) journals for the Netherlands have been analyzed. Due to a language barrier this happened to be impossible for the German journals. Further research could obtain also these country specific journals.

This research has contributed several insights to the Technological Innovation Systems (TIS) theory. As explained by Truffer and Coenen (2012) and Binz et al. (2014), scholars in the field of technological systems of innovation approach have dedicated their efforts mainly towards the energy field. This research has dedicated its efforts towards the healthcare field and in particular the primary diagnostic field. This research has shown that the TIS approach can be applied to the healthcare and primary diagnostic field. But this research has also shown that different indicators are needed in order to analyze the different functions of a TIS approach in a healthcare field. An example is the CE-mark. The CE-marks are awarded to new diagnostic device if they comply with all the regulations. Therefore the CE-mark belongs to the function

'Guidance of the search'. The reimbursement system is also of importance for the implementation process of the emerging in-vitro diagnostic technology and is therefore regarded as an indicator for the function 'Resource mobilization'. Also the indicator 'product introduction' has been obtained in this research, as an indicator for the function 'Entrepreneurial activities', because it is an indicator that entrepreneurial activity took place and also because hardly any results have been found on projects that have been started concerning the in-vitro diagnostic technology. The function 'Creation of Legitimacy' has shown to be highly important for the implementation process of the in-vitro diagnostic technology. Guidelines, regulatory approval and advice are indicators of this function that turned out to be relevant for the in-vitro diagnostic technology. The influence of the function 'Knowledge development' seems to be low in the diagnostic field. A high amount of research has been conducted, especially in the field of clinical chemistry and medical microbiology, but this did not seem to influence the other functions directly.
This research has also shown that motors of innovation can be found in the diagnostic and healthcare field. The influence of the Dutch government (the function 'Creation of legitimacy') has shown to be an accelerator in the Dutch in-vitro diagnostic innovation system. No clear interdependencies were found between the other functions, but the creation of legitimacy turned out to lower the costs of the primary diagnostic system by stimulating other functions of the Dutch in-vitro diagnostic innovation system.

This research is concerned with decreasing the costs of healthcare in the Netherlands. Improvements in the primary diagnostic (innovations) system could lower these costs. Several strengths and weaknesses of both the German and Dutch primary diagnostic innovation system have been identified, analyzed, compared and policy recommendations have been made. But as the interviews of this research showed, all actors in the Dutch primary diagnostic innovation system are already concerned with improving the diagnostic process and the system. These actors could therefore use the findings of this research in order to further improve the Dutch primary diagnostic innovation system.

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9. Appendix

9.1 Appendix A - A country comparison: Germany

In order to choose an adequate country to compare with the Netherlands, several indicators have been measured. These indicators are explained below. A country that satisfies all the indicators is Germany.

Costs of diagnosis
Germany is the only country of which is stated that the costs per diagnostic test (clinical chemistry tests) are lower than for the Netherlands (VGZ, 2013). The primary diagnostic system in Germany is shaped in such a way that only a few large laboratories are sufficient to perform all the diagnostic measurements in Germany. The amount of examinations per laboratory is about seven times as large when compared to the Netherlands, and the costs per examination are substantially lower (VGZ, 2013). This relation between the costs in Germany and the Netherlands is shown in figure 27.

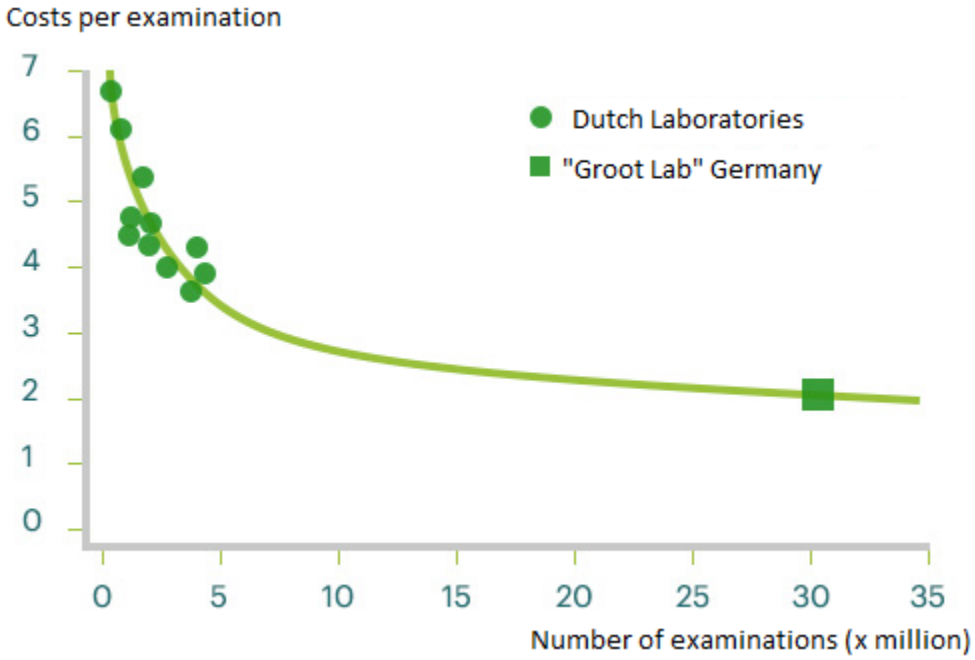

Figure 27. Larger diagnostic laboratories lead to lower costs per diagnostic test (VGZ, 2013)

The low(er) cost per diagnostic test in Germany are also acknowledged by both the Australasian Association of Clinical Biochemists (AACB, 2013). AACB is the major professional society for practicing clinical biochemist in Australia and New Zealand (AACB, 2014). In their annual scientific conference the AACB have stated that in Germany there is a relatively low cost level of testing, because the high degree of centralization of laboratories (AACB, 2013).

Presence of relevant technologies
PoC technologies
Developments concerning the PoC technology in Germany can also be identified. The market for PoC technology systems has grown to 0.9 billion Euros in 2010, which was about a third of the total market for in-vitro diagnostic testing (Junker et al., 2010). The importance of PoC technology in converting the habits of antibiotic prescribing in Germany, as explained by

Altiner et la. (2012), also shows that (developments in) PoC technology becomes more important for the diagnostic system in Germany. The quality of PoC technology has also been reviewed. In a study by Rath et al. (2012), it turned out that developments in PoC technology made it possible to provide accurate and timely diagnosis for infants and children with influenza. So also development and implementation of PoC technology is present in Germany.

Clinical Chemistry
In Germany there is a high degree of centralization of the clinical laboratories (AACB, 2013a). There are five trusts of laboratories that account for about 70% of the laboratory market. This has led to a relatively low cost level of testing.
Developments in the in-vitro diagnostic technology are also notable in Germany. Bioron Diagnostics, for instance, has developed a polymerase chain reaction (PCR) testing device for hospitals, private medical laboratories, veterinary laboratories and other biological investigate facilities (Holzinger, 2011). A study by Kleine et al. (2009) shows that the Joint German Society for Clinical Chemistry and Laboratory Medicine developed and modified certain analyzers in order to improve cell counting and leukocyte differentiating in cerebrospinal fluid controls.

Quality of primary diagnostics
Patient satisfaction in the primary care has been measured by the Robert Koch Institute in Germany (RKI). It turned out that in 2011about 26 percent of the patients was very satisfied with the primary care, and 61.5% was satisfied with the primary care (RKI, 2011). Only 12.3% of the patients were slightly satisfied or not at all satisfied. Table 7 shows these percentages.
In a survey among the physicians themselves, it turned out that at 56% of the physicians, it is possible to get an appointment for the next day/when sick for over 80% of the patients (Schoen et al., 2012). In the Netherlands this is about 61%. Difficulties with paying are lower in Germany than in the Netherlands. In the same survey, it turned out that 21% of the patients often experienced access barriers concerning difficulties with paying. In the Netherlands this is about 42%.

Table 7 Patient satisfaction (RKI, 2011)

Patients		Very Satisfied	Satisfied	Slightly Satisfied	Not at all
Total		26.2	61.5	11.1	1.2
Sex					
	Men	26.7	59.9	11.4	2
	Women	25.9	63	10.7	0.4
Ages					
	18-39 yrs	26.9	57.7	14.1	1.3
	40-59 yrs	25.7	62.4	10	1.9
	60 and older	26.1	65.4	8.2	0.3
Social Status					
	Low	18.4	59.9	19	2.7
	Medium	28	60.6	10.4	1
	High	27.6	63.8	7.8	0.8
Health Insurance					
	Legally	24.3	62.2	12.2	1.3

	Private	36.8	57.3	5.3	0.6

Similarities with the Netherlands

When looking at general information about both the Netherlands and Germany, it can be stated that the differences are quite the same. Sex ratio and age structure do differ to some extend between both countries, but the values are close to each other (Eurostat, 2013). This is shown in table 8. In Germany the population does seem to be older than in the Netherlands, as can be derived from the larger proportion of inhabitants aged 25 to 64 and 64+. The life expectancy is the almost the same for both countries, 81.15 years for the Netherlands and 80.95 years for Germany (Eurostat, 2013). Living conditions and living standards, measured by Gross Domestic Product (GDP), are somewhat higher in the Netherlands than in Germany and the environmental exposure is the same for both the Netherlands and Germany. So when looking at these indicators, it can be stated that both countries do not differ much, although there are some mentionable differences concerning the age structure and living conditions/standards.

Table 8. Similarities with the Netherlands (Eurostat, 2013)

Measurement	How?	Netherlands	Germany
Sex ratio	Women per 100 men	102	103.6
Age structure	Percentage 0-24	29.5	24.2
of population	Percentage 25-64	54.2	55.1
-2012 (percentage)	Percentage 64+	16.2	20.6
	Total	100	100
Life Expectancy	Male	79.3	78.6
at birth (years)	Female	83	83.3
	Mean	81.15	80.95
Living conditions and living standards (GDP) (2012)	Euro: 100	128	123
Environmental exposure	Percentage of Deaths and DALY's attributable to the environment (2004)	16	16

Choosing a country

Germany is the only country that complies with all the indicators. It is especially interesting that statements in the public literature concerning low costs of testing were only focused on Germany. Germany has been referred to as cost efficient in at least four different articles, where other countries were mainly seen as less efficient. Since developments in the in-vitro diagnostic technologies also have been identified and Germany shows similarities with the Netherlands (table 8), Germany is seen as a suitable country to compare with the Netherlands.

9.2 Appendix B – List of Interviewees

Name	Respondent	Date of Interview	Organization	Type of organization
Sjoerd Kruijff	X	12-01-2014	IHSM/MSD	Pharmaceutical company
Albert Zwart (Netherlands)	B	20-01-2014	U-Diagnostics	GP laboratory
Albert Zwart (Germany)		12-05-2014	U-Diagnostics	GP laboratory
Edwin Stuivenwold	D	04-02-2014	NZa	Dutch supervisory body
Lennert Coumans	C	27-02-2014	VGZ	Health insurance company
Roderik Verkaik	E	28-02-2014	BoerCroon	Dutch consultant company
Dagmar Enklaar		28-02-2014		
Matthieu Groenewegen	F	10-03-2014	SHL Groep	GP laboratory
Peter Gisberts	A	08-05-2014	Roche Diagnostics	In-vitro diagnostic manufacturer
Herr Johan van Dalen	G	01-04-2014		
Herr Tim Knipps		01-04-2014	COMED GmbH	IT specialists

9.3 Appendix C – Interview schemes

Interview scheme GP laboratory

1. How would you describe your organization?
    a. What kinds of tests are conducted here?
        i. How many tests are conducted here?
        ii. For how many GPs?
    b. What kind of legal forms do GP labs have, generally?
2. Is there a clear distinction between primary diagnosis and second line diagnosis in Germany?
3. How would you describe the primary care system in Germany?
    a. Who are the most important actors in this system?
4. Could you describe the primary diagnostic process for a patient to me? From the moment the patient feels ill, until the actual diagnosis.
    a. Is this process efficient, both financially as well as when looking at the quality for the patient?
    b. Where does the tissue sampling of the patient take place? At the GP?
    c. How does the sample get to the GP lab??
    d. How does the analysis get to the GP?
5. With whom do GP labs get in touch with directly in their daily business?
    a. And with whom indirectly or sporadically?
    b. How would you describe these relationships?
6. What kind of costs do GP labs have?
7. How are revenues generated at a GP lab?
8. How and by whom are GP labs reimbursed for their activities?
    a. Are GP labs free to choose their place to reimburse their activities?
        i. If not, why?
    b. How would you describe the relationship between a GP lab and a health insurer?
9. Which government agencies are most important in the primary diagnostic system in Germany?
    a. Which laws and regulations do GP labs have to comply with?
10. Are their umbrella organizations for the GP labs in Germany?
    a. Or are there other powerful organizations in the primary diagnostic system in Germany?
11. How would you describe the landscape of GP labs in Germany?
    a. How many GP labs are there in Germany?
    b. Are they united??
    c. How large are those GP labs on average?
12. Which kind of organizations are the competitors of GP labs (for instance hospitals)
    a. How would you describe the relationship between the GP labs and these organizations?

Interview scheme GP

1. How would you describe the primary care system in Germany?
    a. How would you describe the primary diagnostic system in Germany?
2. Could you describe the primary diagnostic process for a patient to me? From the moment the patient feels ill, until the actual diagnosis.
3. What is the role of the GP in the primary care system?
    a. With which parties does the GP get in touch?
        i. How would you describe these relationships?
    b. How would you describe the relationship between a GP and the GP lab?
        i. Is the GP free in its choice of GP labs?
        ii. How long does it take for an analysis to get back to the GP?
4. Are there umbrella organizations for GPs? If so, which one?
5. How does the GP get reimbursed?
        i. Again, is there some free choice or something, or is the GP bounded to, for example, the choice of the patient?
6. Is the current system of high quality for the patient?
7. In the Netherlands, literature has stated the possibility of a one-stop shop model, in which the patient would visit only the GP once in order to get (full) diagnosis. To which extend is this already the case in Germany?
    a. What is needed in order to implement such a system, when looking at..?
        i. Technologies?
            1. PoC?
            2. Clinical Chemistry?
            3. ICT?
        ii. Health insurance?
            1. Could the health insurers cause any problems??
            2. Or could the reimbursement system cause any problems??
        iii. GP labs
            1. Should anything be changed in Germany in order to implement such a one-stop shop model?
            2. Should anything be changed in Germany in order to implement such a one-stop shop model?

Interview scheme Health insurance company

1. How would you describe this organization?
    a. What are its main tasks?
    b. To whom is this organization being held accountable?
2. How would you describe the primary care system in Germany?
    a. How would you describe the primary diagnostic system in Germany?
3. What is the influence of the health insurer on the primary diagnostic system in Germany?
    a. Which organizations have to comply with the framework of the health insurers?
4. Which organizations are most important in the current primary diagnostic system in Germany?
5. Do patient organization exercise any influence on health insurers?
    a. If so, how would you describe this influence?
6. How would you describe the relationship between the health insurer and…
    a. GPs
    b. GP labs
    c. Other kind of organizations capable of analyzing patient tissue for diagnosis
7. Are there free prices of diagnostic tests in Germany, or are there maximum prices just as in the Netherlands?
    a. If the latter is true, where are these included?
    b. How often are these prices recalibrated?
    c. Who determines these prices?
8. In the Netherlands the current primary diagnostic landscape is highly fragmented, which has led to high costs of primary diagnosis and an intertwining of the primary and second line diagnostics. Which solutions do you think are needed in order to solve this problem?
    a. What would be the role of the health insurer?
9. To which extend could technology play a role in these changes?
    a. Could PoC technology be of any importance?
        i. If so, in what way?
    b. Is there other technological development, which could be of importance?
10. To which extend does health insurers have to comply with German and European laws and regulations?
    a. What kinds of regulations are there?

Interview scheme Governmental institution

1. How would you describe this organization?
    a. What are its main tasks?
    b. To whom is this organization being held accountable?
    c. Which organizations have to comply with the framework of this organization?
2. How would you describe the primary care system in Germany?
    a. How would you describe the primary diagnostic system in Germany?
3. How does this organization influence the primary care in Germany?
    a. How does this organization influence the primary diagnostic system in Germany?
    b. How does this organization influence the health insurers?
4. What are the most important actors in the primary diagnostic system in Germany?
5. How would you describe the role of the government in the primary diagnostic system in Germany?
    a. For example, which ministries are of importance, what is their role and which type of organizations do they influence?
6. Do patient organization exercise any influence on the primary diagnostic system?
    a. If so, how would you describe this influence?
7. In the Netherlands the current primary diagnostic landscape is highly fragmented, which has led to high costs of primary diagnosis and an intertwining of the primary and second line diagnostics. When looking at Germany, what should be changed in the Netherlands?
        i. When looking at financing/reimbursement?
        ii. In the diagnostic landscape (for instance, amount of GP labs)
        iii. Concerning the double funding of diagnosis
8. To which extend could technology play a role in these changes?
    a. Could PoC technology be of any importance?
        i. If so, in what way?
    b. Are there other technological development which could be of importance
9. To which extend does this organization has to comply with German and European laws and regulations?
    a. What kinds of regulations are there?

9.4 Appendix D – Operationalization Technological Innovation System

Table 8 Technological Innovation System operationalization (Suurs and Hekkert, 2009; Bergek et al., 2008)

Conceptual Model	*Determinants*	*Indicators*	*Description*	*Sign/Value*
Technological Innovation System	Entrepreneurial Activities	Portfolio expansion	An actor who explores related activities without any previous experience	+1
		Project entry/start	"Technology is explored within a societal context and/or with a commercial goal" (Suurs & Hekkert, 2009, p. 1007)	+1
		Project exit/failure	Exploration activity which has been annulled	-1
		Product introduction		+1
	Knowledge Development	Opinion (critical notes)	Critical notes by actors on institutions and past developments	-1
		Learning by exploring	Research with no direct commercialization orientation	+1
		Learning by doing	Practical research where there is no direct commercialization orientation	+1
		Research projects	-	+1
		Sources of knowledge	If organizations or institutions possess so many data on the markets that they are sources of knowledge	+1
		Desktop/Assessment/Feasibility studies on primary diagnostic technologies	-	+1
	Knowledge diffusion	Networks Coalitions	Co-operation between actors	+1
		Conferences	Meetings, Seminars, Workshops, conferences etc.	+1
		Publishing's	Articles that are published merely to diffuse knowledge	+1
		Fusion	Between companies and laboratories, with the purpose to diffuse data	+1
	Guidance of the search	Classification, Standard setting	-	+1
		Doubt, uncertainty	Uncertainty about the technology's circumstances	-1
		Expectations positive	Positive expectations about the future of the technology	+1
		Expectations negative	Negative expectations about the future of the technology	-1
		Outcome study positive	-	+1
		Outcome study negative	-	-1
		Promises or targets positive	Promises by actors with the power to change institutions, complementing the Technology (Suurs & Hekkert, 2009, p. 1007)	+1
		Promises or targets negative	Negative promises	-1
		Technological guide, Manual	Guidance to support entrepreneurs	+1
		CE-Mark	If new products receive a CE-mark,	+1

			it shows that they can be commercialized	
		Approval	Approval of use of products, or other activities, can guide the technological positively	+1
	Market formation	Niche markets	Protected spaces in which practical experiments can be executed in a market environment	+1
	Resource Mobilization	Investments, Subsidies	-	+1
		Resource refusal	Rejection of (financial support)	-1
		Human Capital	The availability of personnel	+1
		Acquisition	Investments made in order to make an acquisition	+1
		Consolidation	The consolidation of laboratories into only a few	+1
		Outsourcing	Outsourcing of diagnostic activities to other organizations in the primary diagnostic system	-1
		Reimbursement	New products need to be obtained in the reimbursement system in order to become fully implemented	+1
		Capital mobilization	Resources that are literally mobilized to a different organizations	+1
	Creation of legitimacy	Dissent	Disagreeing interests around the technology.	-1
		Lobby or advice pro	"Pressure on actors in power to change institutions, complementing the technology."(Suurs & Hekkert, 2009, p. 1007)	+1
		Lobby or advice contra	"Pressure on actors in power to change institutions, hampering the technology"(Suurs & Hekkert, 2009, p. 1007)	-1
		Regulatory approval	If changes in the primary diagnostic system, for instance acquisitions, are allowed by the regulations.	+1
		Advice	Advice in order to improve the primary diagnostic system	+1
		Guidelines	Guidelines in order to change the primary diagnostic system	+1
Performance	*Implementation of Technology*	Expenditures on the In-vitro diagnostic market		
		Percentage of expenditures on the IVD market of total health care costs		
		Expenditures on the IVD market per capita		

9.5 Appendix E – Description of the Dutch Health care system

The general health care system in the Netherlands has already been illustrated by Nivel (2010). The current health care system in the Netherlands can be described as a further innovation of the original "Bismarckian" social insurance system (Nivel, 2010). The Bismarckian social insurance system is founded in 1883 by a German Chancellor named Otto van Bismarck and refers to a system in which compulsory funding by both employers and employees and this is administered by pre-existing "sickness funds" (OECD, 2011). The system has remained unchanged until 2006. "The reform introduced a single compulsory insurance scheme, in which multiple private health insurers compete for insured persons. "(Nivel, 2010, p. 13). The role of the actors in the health care system has changed radically by this reform (Nivel, 2010). A major change is the shift of the supervision and management of the health insurance system from the government to independent bodies such as the NZa (Nivel, 2010). "The organization of social support has become a municipal responsibility" (Nivel, 2010, p. 13). Also in 2006, the Health Insurance act abolished the distinction between voluntary private insurance and mandatory sickness fund insurance (Nivel, 2010). This has led to competition among multiple private health insurers for insured persons, thereby changing the role of the actors in the system. The main actors in the health care system in the Netherlands, as explained by Nivel (2010), are the health care providers, health insurers and citizens (or patients/health care consumers). Below, in figure 28, the actors and their relationships of the primary diagnostic system are explained.

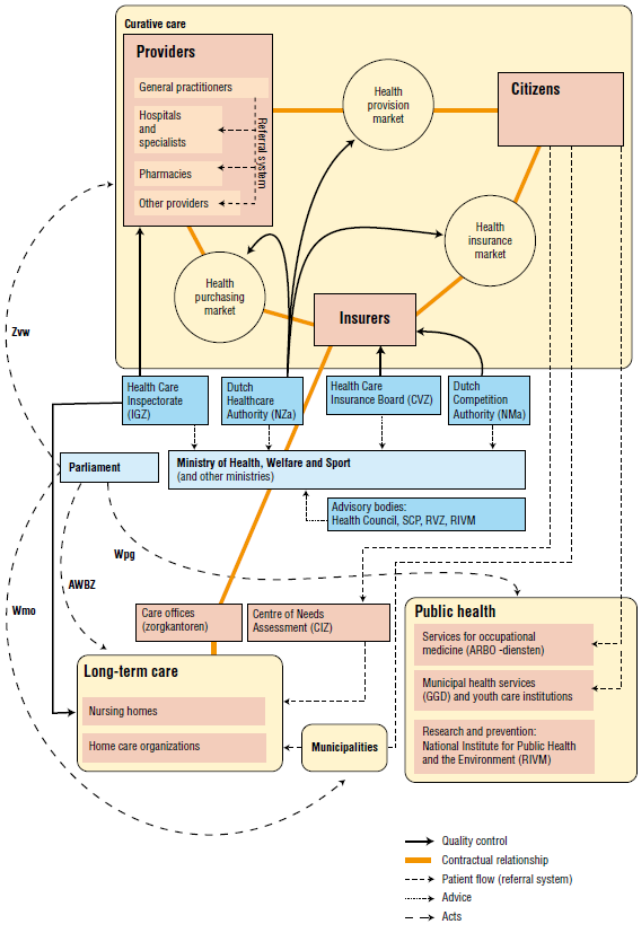

Figure 28. The Dutch health care system (Nivel, 2010)

The government formerly performed the role of direct control of volumes, prices and productive capacity, but now has the role of setting the "rules of the game", and monitoring whether markets are working properly (Nivel, 2010). The health care providers, insurance companies and citizens have become the actual players in the market hereby. As can be seen in figure 28, health care providers are connected to both the patients (health provision market), as well as to insurers (health purchasing market). Citizens and insurers are connected in the health insurance market (Nivel, 2010). In the health provision market, care is offered by health care providers to citizens. In the health purchasing market, health care insurers can negotiate with health care providers on prices, volume and quality of care (Nivel, 2010). In the health insurance market, the basic insurance package is offered by the health care insurers to the citizens (Nivel, 2010). Citizens are obliged to insure themselves in the Netherlands.

Although this research focuses on the primary diagnostic system in the Netherlands, the actors and different markets still apply to the primary diagnostic system. As also stated by Nivel (2010) in their description of the health care system in the Netherlands, the GP functions as a gatekeeper in the health care system. The role of the GP will be explained below, but first the primary diagnostic process is described in short.

9.6 Appendix F – The Diagnostic process in the Netherlands

As explained in the introduction, primary diagnostics refers to diagnostic services that are performed at the request of a primary care provider[15] in the Netherlands (NZa, 2011a). This is shown in figure 29. The basis of the diagnosis is the anamnesis (Eekhof, 2012). Anamnesis refers to symptoms of diseases recognized by GPs, everything spontaneous told by the patient and specific questions by the GP to the patient (Eekhof, 2012). The anamnesis takes about ten minutes (Eekhof, 2012). The first step after the anamnesis in the Netherlands is the application to perform diagnostic tests. Primary care providers in the Netherlands request the applications. Primary care providers refer to GP's, but also to pharmacists, physiotherapists, obstetricians, remedial therapists, dietitians, speech therapists, nurses and care providers in home care, general social workers and primary psychologists (Nivel, 2011) Other possible primary care providers who have the possibility to request primary diagnostic tests are the company doctor, pediatrician and physiotherapist.

The second step refers to the execution of the in-vitro diagnostic examination. In-vitro diagnostics refer to laboratory tests concerning clinical chemistry, medical microbiology, as well as 'Point of Care' (PoC) diagnostics and self-testing by consumers (RIVM, 2013). Several providers, such as hospitals, are capable of executing primary diagnostic tests. Within the execution of primary diagnostic tests, two sub steps can be distinguished; namely the collection of the patient's material (diagnostic sample) and the analysis of the patient's material. Both proceedings can be performed separately at different types of physicians.

The third step refers to the interpretation of the diagnostic tests and advice to the GP. This can be done by the primary care provider who requested the test, but also by a medical specialist who would then obtain a consultative function. The evaluation of the tests eventually leads to a diagnosis, or at least the exclusion of a condition. This could then lead to further treatment in

[15] A primary care provider refers to "a health care practitioner who sees people that have common medical problems (MedlinePlus, 2013)

both the first line (executed by a primary care provider) and the second line (for instance hospitals).

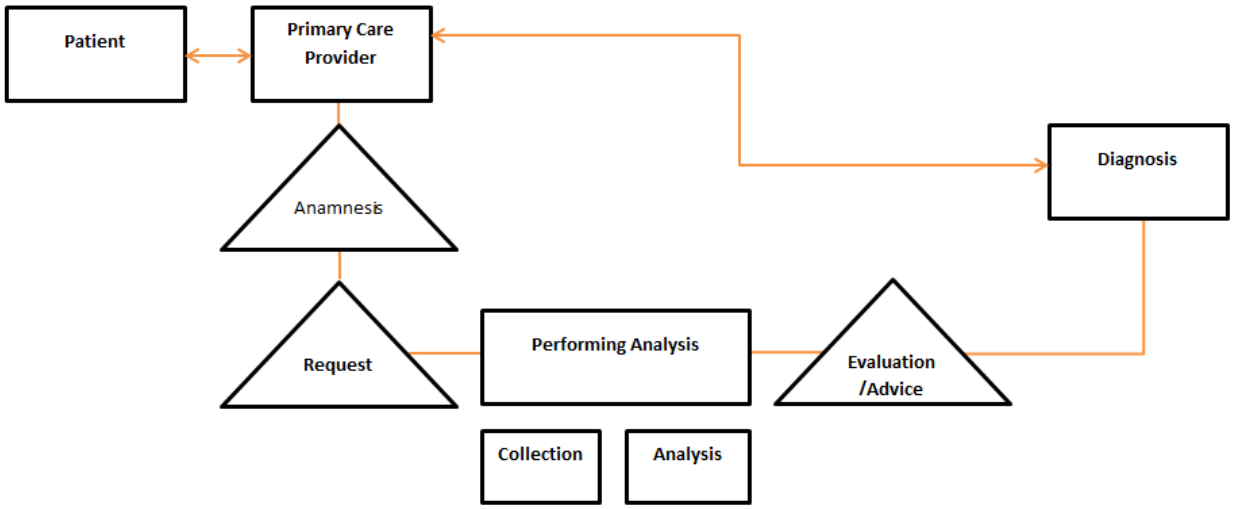

Figure 29 The primary diagnostic process, based on Nivel (2010).

9.7 Appendix G – The Dutch primary diagnostic innovation system

The purpose of describing the primary diagnostic system in the Netherlands is to identify the relevant actors and their relationships in this system. The description of the primary diagnostic process shows that there are various actors operating in a system; in this case the primary diagnostic system in the Netherlands. Several components of innovation systems are illustrated in a framework by Arnold and Kuhlmann (2001). These components will be used as guidance for describing the primary diagnostic system in the Netherlands. The framework of the NIS is shown in the theory section.

Demand

The first component is Demand. Demand refers to both the final demand, as well as intermediate demand of primary diagnosis. In the case of the primary diagnostic system the final demand refers to the patient or the healthcare consumer and the intermediate demand refers to the primary care provider, for instance the general practitioner (Diagned, 2012; NZa, 2011). This is acknowledged by respondent A. As explained above, *the patient (primary care consumer)* seeks for health advice at the primary care provider (NZa, 2011; Vektis, 2013). If health care consumers have somatic or psychosocial complaints, which they cannot remedy themselves, they will seek for health advice at the primary care provider (Vektis, 2013). As explained in Appendix F, this will start with the anamnesis (Eekhof, 2012). Anamnesis refers to symptoms of diseases recognized by GPs, everything spontaneous told by the patient and specific questions by the GP to the patient (Eekhof, 2012) Thereafter the primary care provider could request diagnostic tests in order to be able to underbuilt and complete the diagnosis or to exclude certain conditions (Diagned, 2012).

Primary care providers refer to GP's, but also to pharmacists, physiotherapists, obstetricians, remedial therapists, dietitians, speech therapists, nurses and care providers in home care, general social workers and primary psychologists (Nivel, 2011). Since this research is concerned with in-vitro diagnostics, the focus of the primary diagnostic system will be mainly

on the GP. This is because GPs in the Netherlands have a gatekeeping role (Linden et al., 2003; Vektis, 2013). Citizens with health complaints first go the GP, after which they could receive a referral to specialist care (for instance at the hospital) if needed (LHV, 2011). The GP determines the diagnosis and the associated care (LHV, 2011). The Dutch government increasingly holds the GP partly accountable for their function as gate keeper regarding the diagnosis and further treatment of the patient (Vektis, 2013). This is important for the efficient use of resources, because this allows the proper care to be given in the right place (both geographical and functional). The GP therefore needs to dispose of broad and generalist knowledge of somatic and psychological aspects of health care (Vektis, 2013). Since the services provided at the GP could lead to access to the rest of the health care services, it needs to be accessible for anyone with a health care related issue, seven days a week and 24 hours a day (Vektis, 2013).

In 2014, there were approximately 0.65 GPs per 1000 inhabitants in 2014 (11 000 GPs in total) in the Netherlands. These GP's are spread over 4625 GP practices, 14 Mental health institutions and 97 other institutions (Zorgkaart, 2014a). Moreover, there are 29 diagnostic facilities and 112 GP posts in the Netherlands (Zorgkaart, 2014b). Patients can register with a GP of their own choice, and they can also switch to a different one without restriction (Nivel, 2010). The GP, on its turn, has the right to refuse a patient, if for example the patient lives too far from the GP's practice or if the GP already has enough patients in his population (Nivel, 2010).

The Industrial System

The industrial system can be divided into two parts. The first part includes the developers/manufacturers of in-vitro diagnostic devices. The second part refers to the organizations involved in the actual collection and analysis of patient tissue/blood samples the in-vitro diagnostic process.

In the Netherlands there are several organizations specialized in the development or manufacturing of in-vitro diagnostic devices (Diagned, 2014a). In the Netherlands there is an umbrella organization for manufacturers and importers of in-vitro diagnostic devices, called Diagned (Diagned, 2014a). Diagned represents over 30 manufacturers and importers of in-vitro diagnostic devices, both large and smaller companies (Diagned, 2014a). These manufacturers and importers account for about 90% of the total revenues[16] in the Netherlands (Diagned, 2014a). Diagned is part of the European Diagnostic Manufacturers Association (EDMA) (EDMA, 2014a). The EDMA "is an international, non-profit organization representing the interests of the medical in vitro diagnostics industry in Europe" (EDMA, 2014b).

When looking at the largest in-vitro diagnostics manufacturers worldwide, as described in a global market research by Renub Research (2010), the large in-vitro diagnostics manufacturers are present in the Netherlands (Diagned, 2014b). These companies mainly have subsidiaries in the Netherlands, which are focused on the distribution and sales of medical devices, and also customer services (Abbott, 2014; BeckmanCoulter, 2014; bioMérieux, 2014). The large manufacturers in the Netherlands are Abbott Laboratories (Diagnostic Care), Roche (Diagnostics), BioMérieux, Beckman Coulter, Beckton Dickinson Company, Sysmex, Siemens and Ortho Clinical Diagnostics. Other large in-vitro diagnostics manufacturers in the Netherlands are for example Philips Healthcare (Diagned, 2014b).

There are also smaller companies in the Netherlands; such as Animas. Animas is part of the Johnson & Johnson family and is focused on developing diagnostic devices for Diabetes (Animas, 2013).

[16] Focused on in-vitro diagnostic devices

Respondent A stated that the influence of in-vitro diagnostic manufacturers on the primary diagnostic system is both small and large. It is small in the sense that these manufacturers do hardly influence the decision-making processes by the NZa and government. But manufacturers are seen as strategic partners of their customers (laboratories) and think ahead for solutions to (upcoming) problems in the market. So therefore the influence of manufacturers is also seen as large. In the market, as explained by respondent A, there is both buyer and supplier power between the manufacturers and their customers (mainly laboratories). There is buyer power because the products (diagnostic devices) sold, are highly generic and therefore seen as commodity goods. But there is also supplier power because the problems experienced by the customers are extremely specific. So the added value of the manufacturers becomes important.

Technological development (innovation) by the manufacturers is the result of acquisitions of (small) companies, collaborations and acquisitions of patents of technology transfer offices, but also by trend watching in the market. Also experts in the market are consulted for their knowledge on technological developments. Respondent A labeled this as mutual cross-fertilization. The same interview showed that manufacturers keep in touch with almost all organizations that are engaged in in-vitro diagnostic activities. These organizations refer to GPs, healthcare groups, hospitals, laboratory specialists, GP laboratories, healthcare insurance companies, and other organizations. Manufacturers and hospitals show a more strategic partnership. Next to the sales of devices and tests, hospitals are also considered as strategic partners to manufacturers for research towards new technologies or technological developments.

The second part of the 'Industrial system' refers to the organizations involved in the collection and analysis in the in-vitro diagnostic process. The difference with the primary care providers in the 'Demand' section is the focus of these organizations on purely the execution and analysis of in-vitro diagnostics for the patients of the primary care providers (NZa, 2011a). So these organizations do not provide the anamnesis or the diagnosis to the patients. There are several organizations described by the NZa (2011a);

- GP practices. Next to the applicant of (in-vitro) diagnostic research, GP practices could also be the executor of diagnostic research, by gathering patient materials or analyzing the samples.
- Obstetric practices. Obstetric practices could also be the executor of diagnostic research, by gathering patient materials or analyzing the samples.
- GP labs. GP labs are also referred to as primary diagnostic centers (Eerstelijns Diagnostische Centra, EDC's). This is where laboratory research, imaging diagnostics (for instance echo and MRI) and function testing (ECG, pulmonary function) is being performed, at the request of the primary care provider. An example of this is the Stichting Eerstelijns Diagnostiek Nederland (SEDN). The SEDN supports the GP in the Netherlands with diagnostics for daily practice, from imaging diagnostics to clinical chemistry (SEDN, 2014). A different kind of organization is the Certe group, settle in the North of the Netherlands. Certe is the largest medical laboratory in the Northern Netherlands and has over 850 employees (Certe, 2014b). Other GP labs in the Netherlands are Atal-medial and HAL Friesland. Both organizations are members of the SAN (explained below), but are focused on supporting the GPs in their region (Atal-medial, 2014; HAL, 2014). The GP labs make use of 'prikposten[17]' in order to collect patient material, for instance blood, but a few GP labs made it possible for the patient to have their patient material collected at

[17] A "prik post" is a place where diagnostic samples, such as blood samples, can be taken from the patient. A "prik post" could be located near hospitals or GPs, but also in different places.

home (Atal-MDC, 2014; DCWF, 2014; Certe, 2014a). Interviews have shown that almost all GP labs are foundations, although U-Diagnostics is an example of a GP lab that is a private limited liability company. Respondent B showed that to make use of the tariff lists by the NZa (explained below), a GP lab has to be (part of) a foundation. GP laboratories are not focused on generating profit (De Wildt & Janssen; 2006).

In table 9 some key facts and figures are shown. These data shows the size of the GP labs in the Netherlands. All GP labs shown in table 9 belong to the SAN group (explained below).

Table 9 Amount of diagnostic tests conducted per GP laboratory (Atal-MDC, 2011; MDC-Amstelland, 2012; SCAL, 2012; SHL, 2012; Starlet-DC, 2012; Synergos, 2012)

Organization	Year	Employees	Analyzes	Patient material collections	Revenues (x €1000)
Atal-MDC	2011	900	2.832.361		23.415
Starlet DC	2012			189.079	
SHL Group	2012	867	6.436.816	1.458.575	42.715
MDC Amstelland	2012	91 (FTE)	2.961.488		11.453
Diagnostiek voor u	2012	529	3.032.629		19.210
SCAL Lab	2012	72	1.196.473		6.731

- Hospitals. Hospitals posses their own laboratories, features for imaging diagnostics and function diagnostics. A large share of the hospitals provides both second line diagnostics, as well as primary diagnostics. Hospitals also offer services concerning the collection of patient material, just like the GP labs mentioned above (UMCU, 2014).
- Production partnerships (Productiesamenwerkingsverbanden). These refer to organizations set up by multiple hospitals and mainly refer to laboratories. Generally it concerns a laboratory, but in three cases the production partnership has resulted in a pharmacy (linked to the hospital). There are eighteen production partnerships in the Netherlands.
- Independent Treatment Centers (Zelfstandige Behandelcentra, ZBC). These centers have the capabilities to perform all forms of diagnostics.
- Care Groups. Care groups are described as organizations, which conclude contracts with health insurers in order to coordinate and perform the chronic care in a region in order to increase the quality of care (Encyclo, 2014). The composition and supply of care groups differ, but they have the capabilities to offer a combination of imaging diagnostics, function diagnostics and laboratory research.

In the Netherlands there are around 60 to 70 hospital laboratories focused on the primary diagnosis, and there are circa 23 EDC's located in the Netherlands. These laboratories and EDC's differ in their size and catchment areas (NZa, 2011a).

The Political System

Government Ministries

When looking at the Dutch health care system, several government ministries possess some influence. The Ministry of Health, Welfare and Sport, a separate administrative body, develops policies in order to ensure the well-being and health of the population in the Netherlands (Ministerie van VWS, 2014) To guarantee the access to a high-quality system of health care

facilities and services is one of the major objectives of this ministry (Den Exter et al., 2004; Ministerie van VWS, 2014). But the provision of health care services is largely based on private initiative, which leads to a limited role of the government in the delivery of health care services (Nivel, 2010).

The second relevant government ministry is the Ministry of Social Affairs and Employment. The tasks of the Ministry of Social Affairs and Employment refer to the stimulation of employment, the encouragement of modern labor relations and to oversee social security policy (Ministerie van SZW; 2014). "The Ministry has its own responsibilities for health-related social security schemes covering sickness benefits and disability benefits. These benefits are outside the health insurance scheme, although they are funded by contributions jointly paid by employers and employees." (Nivel, 2010, p. 24)

Supervisory Bodies

The Dutch Health Care Authority (NZa) is an independent administrative body in the Netherlands (NZa, 2014a). Its tasks are defined in the Health Care Market Regulation Act[18] (NZa, 2014b). The NZa is responsible for supervising the three health care markets in the Netherlands; namely the health provision market, health insurance market and the health purchasing market (Nivel, 2010). The NZa is thereby authorized to impose tariff- and performance regulation. The NZa may request adapting price setting in line with NZa rules of those players that have obtained significant market power and have raised their prices too highly (NZa, 2014a). The NZa also has the authority to set up general rules for healthcare providers and health insurers to increase the transparency of the market for consumers (NZa, 2014a).

The Health Care Inspectorate (IGZ) is an independent organizations that supervises the accessibility and quality of health care in the Netherlands (IGZ, 2014). The tasks of the IGZ are to investigate complaints and accidents in health care, to enforce statutory regulations on public health and to take appropriate measures (IGZ, 2014). The IGZ is also an advisory body to the Minister of Health, Welfare and Sport.

The Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek (SKML) is founded in order to monitor the quality of the clinical chemistry laboratories in the Netherlands (NVKC, 2014c). The main goals pursued by the SKML are (1) the organization of external quality monitoring (relating to execution and interpretation of medical laboratory research), (2) the development and publishing of calibration and reference materials for the diagnostic procedures, (3) the spread of new, relevant knowledge for related to medical laboratory tests and their scientific basis, (4) the improvement of the quality by providing advice to primary diagnostics in general and GPs in particular, (5) the quality evaluation of diagnostic test systems and (6) the organization of meetings with participants (NVKC, 2014c).

The "Rijksinstituut voor Volksgezondheid en Milieu" (RIVM) has studied the technical files provided by the manufacturers of in-vitro diagnostics in order to assess the quality of the different parts of the documentation that manufacturers have to submit in order to commercialize their products (RIVM, 2014). The RIVM has also proposed to change the European classification system for in-vitro diagnostics (RIVM, 2014). This is because the current classification system has some flaws, which could be corrected with the proposal of the RIVM. At last, the RIVM has also conducted studies concerning new developments and usage in the field of PoC technology (RIVM, 2014).

The Dutch competition regulator (Nederlandse Mededingingsautoriteit, NMa) has the general task to enforce fair competition in all sectors of the Dutch economy, for instance in the health care sector (Nivel, 2010). Since April 1st of 2013, the NMA has joined with the

[18] Wet Marktordening Gezondheidszorg, Wmg (Nivel, 2010)

Onafhankelijke Post en Telecommunicatie Autoriteit (OPTA) into the Autoriteit Consument & Mark (ACM) (ACM, 2014a. The ACM has come up with rules for the health care market in the Netherlands concerning the collaboration of health insurers, mergers between health institutions such as GP labs, and the collaboration of care groups (ACM, 2014b.

Advisory Bodies

Next to the importance of government ministries and supervisory bodies, also advisory bodies have an influence on the primary diagnostic system. This is because in the Netherlands, decision-making is characterized by consultation and consensus between the government and relevant stakeholder groups (Nivel, 2010). The role of advisory bodies in this process is important.

An important advisory body is the Health Council (Gezondheidsraad), which is a statutory advisory body to the government (the Ministry of Health, Welfare and Sport) (Gezondheidsraad, 2014). The Health Council gives advice on the scientific state of the art in health care, public health, medicine and environmental protection (Gezondheidsraad, 2014).

The Council for Public Health and Health care (Raad voor de Volksgezondheid en Zorg, RVZ) is an independent advisory body, installed by the Minister of Health, Welfare and Sport (RVZ, 2014a). This RVZ has been installed for strategic advice on health care and welfare policy (RVZ, 2014a). In general, advice is given on request by the minister (for instance of Health, Welfare and Sport), but the Council could also take the initiative itself (RVZ, 2014b).

Intermediaries

Brokers

Brokers are described as agents who facilitate the process of knowledge and technology transfer across people, organizations and industries (Howells, 2006).

Patients could unite into patient organizations. Patient organizations represent the interests of the patients, and thereby influence the diagnostic system; by for instance influencing the decision-making in the political system (Artsennet, 2014; NPCF, 2014) Patient organizations are focused on representing the interests of the affiliated health care consumers (Artsennet, 2014; NPCF, 2014). Specific diseases or disorders, such as diabetes, are for example binding factors for patients to unite in to patient organizations (Zorgkaart, 2014c.). Regions are also binding factors for patients, which has led to the establishment of regional organizations such as Zorgbelang Groningen and Cliëntenbelang Amsterdam (Zorgkaart, 2014c).). There is also an overall organization for Dutch patients: the Dutch Patient Association (Nederlandse Patiënten Vereniging, NPV) (Zorgkaart, 2014c).

There are also umbrella organizations for primary care providers. An example of this is The Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) (NHG, 2014a). The intention of the NHG is to provide the general practice with maximum scientific support and thereby facilitating the work of the individual GP (Nivel, 2010). The NHG develops guidelines for the GP's concerning inter alia pharmacotherapy, automation in the general practice and the quality and safety of primary care (NHG, 2014a). The NHG also develops the NHG-standards. These standards have the purpose to support the medical policies in the daily practice of the GP (NHG, 2014b). So these are protocols to which the GPs in the Netherlands could act on. The NHG membership is voluntary, but still a major part of the Dutch GPs are members. Other examples of umbrella organizations are the Landelijke Huisartsen Vereniging (LHV), which is focused on representing the interests of the GP's in the Netherlands (LHV, 2014a). The LHV has lobbied, for example, for the financing and reimbursement of the GPs in the Netherlands (LHV, 2014b).

The GP practices, production partnerships and GP labs could also belong to so called umbrella organizations. An example of such an organization is the Samenwerkende

Artsenlaboratorium Nederland (SAN), which is an interbranch organization for the medical diagnostics (SAN, 2010). 23 GP labs and diagnostic centers, across the country, are member of the SAN, which accounts for about 4000 employees. They are committed to 85% of the GPs in the Netherlands, and about 65% of the obstetricians (SAN, 2014). The purpose of the SAN is to provide the GPs with the best optimal diagnostic facilities (SAN, 2014).

The Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde (NVKC) is a scientific professional association of laboratory specialists (NVKC, 2014c). The main goals of the NVKC are to (1) facilitate the further development and quality improvement of the individual patient care, (2) to broaden en deepen the discipline of clinical chemistry, (3) prepare new generation of laboratory specialists for their future role in the health care system, (4) preparing the new generation of laboratory specialists for the optimal use of laboratory diagnostics and (5) creating a challenging work/learning environment for the new generation of laboratory employees and analysts (NVKC, 2014c)

The Nederlandse Vereniging voor Medische Microbiologie (NVMM) is only focused on the medical microbiology. This means that the NVMM tries to promote activities in the area of prevention, diagnostics, study of pathogenesis, treatment and epidemiology of microbial diseases (NVMM, 2014). The NVMM also promotes scientific activities concerning medical microbiology, training activities for the medical microbiology, the quality of the practice of medical microbiology and facilitating the medical microbiologist it its tangible and intangible interests (NVMM, 2014).

Zorgverzekeraars Nederland (ZN) represent the interests of the health insurers in the Netherlands (ZN, 2014a). When looking at the primary diagnostic system, the ZN is strongly committed to the purchasing of high quality care and diagnostic processes, as well as the control of the high costs (financing of the primary diagnostic system in the Netherlands) and an efficient implementation of the diagnostic processes (ZN, 2014a; ZN, 2014b).

The Health Care Insurance Board (College voor Zorgverzekeringen, CVZ) is an independent organization and acts regarding the Health Insurance Act (Zorgverzekeringswet, Zvw) and the Exceptional Medical Expenses Act (Algemene Wet Bijzondere Ziektekosten, AWBZ) (CVZ, 2014). The CVZ has three important tasks. At first, "the Board must make sure that the health insurers explain regulations and the implementation of the Health Insurance Act and the Exceptional Medical Expenses Act uniformly, in particular since the limits of the benefits package may be ambiguous and prone to different interpretations."(Nivel, 2010, p. 27) The second task is to manage and administer the Health Insurance Fund al also the General Fund for Exceptional Medical Expenses (Algemeen Fonds Bijzondere Ziektekosten, AFBZ) (CVZ, 2014). The third task is to advise the Ministry of Health, Welfare and Sport on the basic health insurance package (CVZ, 2014).

Other relevant organizations are care groups, such as the Zorggroep Eerste Lijn (ZEL, 2014). The goal of this care group is to improve the quality of the primary care at the GP (ZEL, 2014).

Research institutes:

In the Dutch healthcare system, and primary care system, several knowledge and research institutes can be identified. One of the largest institutes is the National Institute for Public health and the Environment (Rijksinstituut voor de Volksgezondheid en Milieuhygiëne, RIVM) (Nivel, 2010). The RIVM is a major adviser to several ministries, such as the Ministry of Health, Welfare and Sport. It mainly provides policy support to the Ministry of Health, Welfare and Sport, divided into key public health areas (Nivel, 2010; RIVM, 2014) One of these key areas is "In-vitro Diagnostics" (RIVM, 2014). The RIVM also conducts patient oriented diagnostic research concerning bacteriology, parasitology and virology (RIVM, 2014).

A different research institute is the Netherlands Institute for Social Research (Sociaal en Cultureel Planbureau, SCP). Formally it is subordinate to the government, but it also carries out independent research (Nivel, 2010). The SCP does not focus its research on (in-vitro) diagnostics as well as the RIVM, but several studies concerning primary care (mental health mainly) have been conducted by the SCP (SCP, 2014). The tasks of the SCP are inter alia to describe the social and cultural situation in the Netherlands, the forecasting of development and to provide information and evidence for policy-making as well as to evaluate government policy (Nivel, 2010).

Other examples of research institutes are Sanquin and Caphri (part of University of Maastricht) (Sanquin, 2014; Cahpri, 2014). Sanquin conduct research in the field of plasma drug immunology, cell biology, blood-borne infectious diseases and hematology (Sanquin, 2014). One of the fields of research of Caphri is "Diagnosis and Treatment of Frequently Occurring Diseases in Primary Care". Caphri, for example, conducts research towards the diagnosis of respiratory tract infections (Caphri, 2014).

The Educational System

In the Netherlands there are several educational organizations focused on primary diagnostics. In the Netherlands there are eight medical faculties, which are connected to eight university hospitals (teaching hospitals) (Anno73, 2014). Students can be trained to become a GP at these faculties.

There are also educational organizations in the Netherlands focused on in-vitro diagnostics. At the Vrije Universiteit (VUMC), there is a department for clinical chemistry (VUMC, 2014). This1 department is concerned with conducting research for clinical chemistry (VUMC, 2014). Dekker and Meijer (2009) have described the academic program Medical natural Sciences at the VU and VUMC. "In this program students receive training in exact sciences (physics, chemistry and mathematics) in a strong medical context, combined with basic courses in biomedical sciences and a program of general academic skills" (Dekker & Meijer, 2009, p.155). The main goal of both the bachelor and the master program is to provide the students enrolled in this program with the skills to conduct research in the fields of biomedical physics, medical physiology and clinical chemistry (Dekker & Meijer, 2009).

There are also education organizations located in the Netherlands focused on educating medical laboratory research. Such an organization is Saxion Technische Opleidingen en Studieroutes, located in Deventer/Enschede in the Netherlands (Saxion, 2014). At the Technische Universiteit Eindhoven (University of Technology Eindhoven) there is a master program called Medical Engineering, and a part of this program consists of clinical modules focused on clinical chemistry and medical devices (TUE, 2014). In order to become a professional registered laboratory specialist (Clinical chemistry), first a master degree in Medicine, Pharmacy or Biochemistry or Medical Biology has to be obtained (NVKC, 2014a). These master degrees make it possible for people to enroll in the program to become a registered clinical chemistry laboratory specialist (NVKC, 2014a). All over the Netherlands there are training places for the clinical chemistry laboratory specialist program, mainly at hospitals (NVKC, 2014a).

Infrastructure

Infrastructure refers to the standards & norms, health insurances and mobility/quality of the primary diagnostic system. This is because the health care market is highly regulated, health insurances play a significant role and the mobility and quality is of importance for the patients (Field, 2008).

Standards and Norms

As explained by Diagned (2012), the quality of the in-vitro diagnostics rests on two cornerstones; namely safe and effective diagnostic tests on the one hand and professional use on the other hand. The quality demands for both the product (devices) as well as use are recorded in laws and regulations; "Besluit IVD", "Besluit medische hulpmiddelen" and "Kwaliteitswet zorginstellingen" (Diagned, 2012; Overheid, 2014a; Overheid, 2014b). The industry (manufacturers) and laboratories are all responsible for proper and safe usage of in-vitro diagnostics. The IGZ supervises the compliance of the relevant actors to the laws and regulations (Diagned, 2012).
The IGZ reports that in-vitro diagnostics intended for the Dutch trade market have to be registered with the Centraal Informatiepunt Beroepen Gezondheidszorg (CIBG) (IGZ, 2014). Also the manufacturer has to register with the CIBG (IGZ, 2014). The CIBG is an executive agency of the Ministry of Health, Welfare and Sport (CIBG, 2014). The CIBG collects and processes (certified) data and extradites these data, mainly for the health care sector in the Netherlands (CIBG, 2014). All the administrative registrations are administered by Farmatec (IGZ, 2014). The manufacturer is responsible for the registration of both the company as well as the product (IGZ, 2014). But the confirmation of the registration by the CIBG is not based on a qualitative review of the product, the manufacturer first has to comply with the quality and safety standards for in-vitro diagnostics imposed by the government (IGZ, 2014).

For the GPs there are the NHG guidelines and standards as explained above (Nivel, 2010). These guidelines and standards refer to the best treatment options or diagnostic services as explained by the NHG (NHG, 2014b).

Supporting devices and resources for the in-vitro diagnostics have to comply with the CE marking (RVO, 2014). The CE marking is a guideline (98/79/EEG) for manufacturers of supporting devices and resources for the in-vitro diagnostics and the products that are subject to this guideline have to meet several essential criteria (RVO, 2014). The manufacturer or importer is responsible for meeting these criteria and for the administrative processing. If these criteria are met, then the products will receive the CE marking, and free trade within the European Union becomes possible. The controlling authority for this guideline is the IGZ, and the ministries involved are the Ministry of Health, Welfare and Sport and Pharmaceutical Affairs and Medical Technology (part of the Ministry of Health, Welfare and Sport) (RVO, 2014). The diagnostic products have to comply with the European Medical Device Directives (Medical Device Directive 93/42/EEC, Active Implantable Medical Devices 90/385/EEC and In Vitro Diagnostic Medical Device Directive 98/79/EC) (European Commission, 2014). Respondent A showed that newly developed diagnostic devices have to show their efficacy, safety, medical value and budget impact in order to get approved.

Diagnostic laboratories have to be certified with the CCKL mark (NVKC, 2014b). This quality mark is developed by the "Coördinatie Commissie ter bevordering van de Kwaliteitsbeheersing op het gebied van Laboratoriumonderzoek in de Gezondheidszorg" foundation (CCKL foundation), in order to improve the quality of the laboratory research in the health care system in the Netherlands (NVKC, 2014b). The quality mark shows that the laboratory handles the offered patient materials carefully and discreet (Elkerliek, 2014).

Next to the CCKL mark, the NVKC also reports on the existence of several (essential) guidelines applicable to clinical chemistry (NVKC, 2014d). The essential guidelines refer to professional standards for the clinical chemistry, blood sampling, recommended method for microscopic assessment, sharing of laboratory results, and consultation by specialists (NVKC, 2014d). The other guidelines refer to different aspects of clinical chemistry and in-vitro diagnostics (for example, also PoC testing) (NVKC, 2014d).

Health Insurance

Everyone in the Netherlands is obliged to have a health insurance (Rijksoverheid, 2014a). A health insurance consists of the basic health insurance, which is obligatory to have, and the supplementary insurance (Rijksoverheid, 2014a). The government decides what is obtained in the basic package of the basic health insurance in the Netherlands (Rijksoverheid, 2014a). Citizens pay a fixed contribution to the health insurance in order to receive services obtained in the (basic) health insurance (Rijksoverheid, 2014a).
In the Netherlands there are four large insurance concerns for health insurance companies that account for approximately 95% of the health insurance market in the Netherlands (Kassa, 2013). These organizations are CZ, Menzis, UVIT and Zilveren Kruis Achmea (Kassa, 2013). In total, there are 9 insurance concerns, which offer approximately 35 health insurances (Independer, 2014). The main tasks of the health insurance companies, as explained by respondent C, are to acquire enough health care for their clients, but also to influence the costs, quality and customer experience of the health care system. Respondent C saw it as a main task of the health insurance company to provide the health care market, and the diagnostic market, with incentives to operate more efficiently.

Mobility
Almost every citizen in the Netherlands is able to travel to a GP within 15 minutes (Zorgatlas, 2013). The shortest travelling times occur in the cities, where many citizens are able to go to a GP within 3 minutes (Zorgatlas, 2013). The longest travelling times occur in the provinces Friesland, Groningen, Drenthe and Flevoland (Zorgatlas, 2013). GPs can usually be visited within two days in the Netherlands (Nivel, 2010).

Framework Conditions
Framework conditions refer to the financial environment, taxation and incentives, and propensity to innovation and entrepreneurs (Arnold & Kuhlmann, 2001).
In general, there is the Dutch Tax and Custom Administration (Belastingdienst, Tax Office) (Nivel, 2010). The Tax Office has the task to levy and collect taxes, as well as social health insurance (employer) contributions, and to pay out the health care allowance (zorgstoeslag) in order to compensate the lower-income groups for an excessive premium burden (Nivel, 2011).

Financial Environment
Important in the financial environment is the funding and reimbursement of the relevant actors, since this is one of the described problems described by the NZa of the Dutch primary diagnostic system (NZa, 2011). The financing will be described per actor, because the funding systems differ per health care provider (NZa, 2011).

General Practitioners. The primary diagnostic activities executed by the GP are mainly reimbursed according to the Modernization and Innovation (M&I) module (Vektis, 2013). This module makes it possible to charge several services such as diagnostics like ultrasound examination for which free pricing is applied (NZa, 2011). Additional diagnostic procedures by the GP are ought to be covered by the subscription rate per patient or can be charged per consult (NZa, 2011).

Obstetricians. Obstetricians receive a subscription rate per patient. Next to the subscription rates, obstetricians could charge maximum tariffs for specific diagnostic procedures, such as ultrasound examinations (NZa, 2011).

GP labs (EDC's). GP labs were budget funded until 2014[19] (NZa, 2011; Kamerbrief, 2013). The funding of the GP labs can be divided into analysis costs (laboratory analysis of patient materials), function examination and order costs (NZa, 2011). The reimbursement of

[19] see section "2015: A new way of funding the GP labs"

costs for analysis consists of revenues from fixed rates for approximately 700 different operations (NZa, 2011). The reimbursement of the remaining types of research (mainly function examination) consists of a part of the revenues from the concerned fixed rates, but excluding the location costs and interest component (NZa, 2011). The order costs consist of costs that can be attributed to the costs of taking away patient material, availability fees and costs for registration and billing. This reimbursement is incorporated in a price per order. There are also costs involved when the laboratory does not perform the diagnostic operations at their original location (Toeslag voor de deconcentratiegraad). The tariffs claimed by the EDC's are obtained in a list called the "Tarievenlijst Eerstelijnsdiagnostiek", established by the NZa (NZa, 2013a). However, as of 2014, the budget funding changed into performance funding, as explained the chapter "2015: A new way of funding the GP labs" (NZa, 2013b).

Production partnerships (Productiesamenwerkingsverbanden). Until 2012 the production partnerships were (partly) budget funded. They were funded according to a so called cashier functionality (kassiersfunctie), because they collaborate with affiliated hospitals. So these production partnerships were funded by the hospitals, which could claim both the labor costs of medical specialists and costs for location. But since 2012 the cashier functionality has expired and the production collaborations are now funded based on performance funding (NZa, 2011).

Hospitals. As of the year 2012, also the hospitals changed from a situation of budget funding to a situation of performance funding (NZa, 2011). Tariffs for the primary diagnostic services apply also to the ELD list, which shows the maximum prices for these services (NZa, 2011).

Independent Treatment Centers (Zelfstandige Behandelcentra, ZBC). ZBC's are completely funded based on performance funding. Primary care and diagnostic services by ZBC's also apply to the ELD list, which shows the maximum prices.

Care groups. Care groups are mostly focused on chronic diseases/disorders and the primary diagnostic services during the treatments are excluded from the performance (NZa, 2011a). This exception does not apply to the care providers who have already obtained the primary diagnostic services in the policy guideline "Innovatie ten behoeve van nieuwe zorgprestaties" (Innovation to achieve new care services) (NZa, 2011a).

The NZa has released the price list (Tarievenlijst Eerstelijnsdiagnostiek; ELD-list) for the primary diagnosis in the Netherlands as of April first 2013 (NZa, 2013a). As explained above, the prices in the ELD-list are the tariffs that (primary) care providers can charge for the services they deliver in the primary diagnostic sector (NZa, 2013a). The reimbursement of laboratory research in the primary diagnostic system is arranged between the health insurer and the laboratory (Diagned, 2012).

The Ministry of Health, Welfare and Sport has been advised by the NZa in 2013, to change the reimbursement system from fixed prices to maximum pricing. The NZa assessed the Dutch primary diagnostic market as competitive enough to ensure well-balanced market forces, and thereby the absence of misuse of market position by the relevant stakeholders (Kamerbrief, 2013). Eventually this has resulted into a maximum pricing system (see the section '2015: A new way of funding the GP labs' below).

9.8 Appendix H - 2015: A new way of funding the GP labs

2015: A new way of funding the GP labs

As explained in the section *Financial Environment*, the production partnerships and hospitals were budget funded until 2012 (NZa, 2011). Thereafter these organizations became performance funded (NZa, 2011). The reason for this change was to create incentives for health care providers in order to optimize the healthcare and logistic processes in a more efficient way. It is also an incentive for health care insurance companies to choose for the most efficient health care providers, which would decrease costs of care (Ministerie van VWS, 2011). The GP labs were budget funded until the first of January 2014. In 2014, the NZa implemented the policy guideline 'Eerstelijnsdiagnostiek' (TB/CU-7041-03). In this policy, it has been determined that maximum tariffs will be used for the suppliers and that the transition will be made from budget funding to performance funding for GP labs (NZa, 2013b). The year 2014 will be used as a year of transition (NZa, 2013b). This transition model enables the GP labs to adjust their business operations and management to the performance-funding model, and to generate 15% equity (NZa, 2013b). The transition model will also minimize any budgetary consequences during the transition period (NZa, 2013b; SAN, 2013). The GP labs are allowed to grow with 2.5% every year (Daris, 2013). The maximum tariffs have also been recalibrated on the basis of a new investigation regarding the costs of the diagnostic services. This has not been done since 2003, however the tariffs have been indexed yearly (NZa, 2013b). Due to technological developments, costs of the diagnostic services have dropped over the years but the tariffs have not been changed according to these drops (NZa, 2013b). In other words, prices were too high, and the market was old and archaic.

The reason for this policy guideline is the persistent criticisms on the funding of the GP labs (Engelenburg, 2013). In the situation of budget funding, the GP labs had no incentives to operate more efficient, because they worked with fixed tariffs and a budget (Engelenburg, 2013). If GP labs operated more efficient and did not use the entire budget, the budget would have been cut by the health insurers for the next year (Engelenburg, 2013). So if they operated more efficient, it would lead to lower revenues in the next year. In other words, there wasn't any incentive to act more efficient. Hospitals, on the other hand, had discovered in-vitro diagnostics as an extra source of revenues a few years ago to fund expensive other 2nd line services (Olsthoorn, 2011). But this has led to a situation of separated files by the different health care providers, and unusable and badly exchangeable data between them (Financieel Dagblad, 2011). Therefore experts (Ron Kusters, a clinical chemist and professor economic effects in laboratory diagnostics, and Maarten Ijzerman, professor health technology and service research) have mentioned the importance of infrastructure for the laboratory diagnostics (Financieel Dagblad, 2011). An example could be a situation in which the hospital would perform all the diagnostic analyzes for the GPs, which would lead to cost effective and high quality analyzes (Financieel Dagblad, 2011).
Other possibilities in order to reduce the costs of diagnostics are mergers between GP labs and/or hospitals (Engelenburg, 2011). Already some hospitals have merged, as well as several GP labs. In combination with the performance funding, mergers make it possible for GP labs to obtain economies of scale, thereby work more efficient and decrease the costs of their diagnostic services (Engelenburg, 2011). Volume is important in this sector, because 85% of the operations performed in GP labs are routine based. So the higher the volume, the lower the cost per test (Engelenburg, 2011). This is already the case in both Germany and Belgium, but as can be learned from both countries these lower costs per test could result in an increase of examinations (Engelenburg, 2011). The lower costs per test would then be compensated by the higher amount of examinations; so the cost of primary diagnostics would then still not decrease in costs (Engelenburg, 2011). But health insurers will now be able to choose between the most efficient GP labs or hospitals, which will be another incentive to operate more efficient (Engelenburg, 2011). Respondent C showed that health insurance companies also control the volume of the diagnostic tests because one of the main tasks of the company is the procurement of healthcare. So the health insurance companies in the Netherlands control both the volumes and costs of the diagnostic market.

9.9 Appendix I – The German Health care system

The German health care system rests on three founding principles, established by Otto von Bismarck in 1883 (Civitas, 2013). These principles are solidarity, subsidiarity and corporatism. Solidarity refers to the responsibility by the German government to take care of those who are unable to participate in the private health insurance sector and thereby securing universal access to health care (Civitas, 2013).
"Subsidiarity suggests a decentralized system under which policy is implemented by the smallest feasible political and administrative units in society"(Civitas, 2013, p.2). Corporatism refers to the democratic character of the system; both employers and employees are represented (in groups and on the governing boards), on both the national and regional level (Civitas, 2013). This, on its turn, brings along some problems, because vested interest could differ heavily between the represented groups. "Health care policies are therefore often fragile, watered-down in order to protect the cohesion of the central government coalition and in danger of being reversed once the balance of political power changes"(Civitas, 2013, p.3).
In order to ensure social security in cases of illness, the basic principles of social rights have been used as a framework (Döring & Paul, 2012). This framework has to be used by the health care providers and the health insurance companies (Döring & Paul, 2012). The German state can be seen as a welfare state, and these principles of the welfare state are based on the Federal Republic of Germany's Basic Law (Grundgesetz) (Döring & Paul, 2012). The Grundgesetz specifies that the state is obliged to guarantee social justice and equal participation in society (including appropriate treatment) to all citizens (Döring & Paul, 2012). The German healthcare system is a mixed public and private system (Porter & Guth, 2012). The German healthcare system makes use of statutory plans (Porter & Guth, 2012). "Statutory plans are legally required to underwrite every applicant, and participation by citizens in statutory insurance is mandatory unless an individual is covered by the private system"(Porter & Guth, 2012, p.53).

In the past, many reforms have been applied in the healthcare system in Germany, but according to Porter & Gurth (2012) still some reforms will have to be made. The past reforms have mainly focused on price controls and structural changes in the insurance system. The German system is suffering from a fragmented healthcare structure and this has led to very high patient volumes and healthcare provider contacts, as well as a surplus of healthcare providers offering too diverse service lines. According to Porter & Gurth (2012), the health care in Germany is too local instead of complex cases that are addressed in regional centers. This has led to a situation in which the overall volume of care is great, but where providers lack volume at the level of individual medical conditions. Healthcare providers do not feel the urge to change, because of the structure of the licensing laws, resulting in quasi monopolies for incumbent providers (Porter & Gurth, 2012).

The German healthcare system consists of the State, the cost bearer (Health insurance companies), service providers (Healthcare providers) and insures (citizens) (Döring & Paul, 2012). The organizations report to the Federal Ministry of Health. The Federal Ministry of Health drafts laws, regulations and administrative provisions, but is also responsible for the supervision to the federal agencies involved and for appointing an expert commission in order to evaluate the development of public health (Döring & Paul, 2012). The State also directly funds facilities such as university clinics and state psychiatric hospitals. "The highest state authorities are the ministries of social affairs or health, to which, in turn, other state authorities, such as the state public health offices, report"(Döring & Paul, 2012, p.49). The public health offices supervise if organizations such as health insurance companies are compliant with the federal and state laws. Municipalities enforce the legislations locally, focused on the healthcare

professions, distribution of foodstuffs and medical products, contagious disease prevention and control, and health education and counseling (Döring & Paul, 2012).

9.10 Appendix J – The German primary diagnostic innovation system

The German primary diagnostic system

Demand

The first determinant that will be discussed, is Demand. As for the Netherlands, also in Germany the determinant Demand in the primary diagnostic system refers to both patients as well as GPs.

GPs

The Federal Ministry of Health (Bundesministerium für Gesundheid, BMG) describes the relationship between the GP and the patient as the core of the German health care system (BMG, 2013a). If patients are in need of medical care, they could visit every doctor they trust and who is certified to help the patient (BMG, 2013a). So patients are able to freely choose their GP. The BMG states that the GP has a central role in the health care system in Germany, with which is meant that the GP is the first point of contact for the patient and that the GP acts as a coordinator for further treatment (BMG, 2013a). The GP has a broad basis of basic knowledge, knows the history and circumstances of the patients and therefore is able to judge the situation properly (BMG, 2013a). The GP discusses the further treatment and actions with the patient. But according to respondents G the traditionally primary care providers (GPs mainly) in Germany do not have a formal gatekeeper function. The first physician, who is consulted by a patient, can be both a GP, as well as a specialist (Schlette et al., 2009; Respondents G, 2014). This shows that it is the patient who can decide what kind of physician is the right one in order to solve their medical problem(s), instead of the GP (Linden et al., 2003). The patient even has the possibility to see more than one physician in order to seek for the optimal solution (Linden et al., 2003). Respondents G has shown that the specialists are not located in the hospitals, as in the Netherlands, but most of them have their own practices locally. These practices could be located next to GP practices.

About 43% of the physicians in Germany work in ambulatory care, but the amount of GPs is decreasing (EUprimarycare, 2014). In Germany there were about 0.59 GPs per 1000 inhabitants in 2014, (Statista, 2014). Absolute numbers show that there were about 48 920 working GPs in 2012 in Germany (KBV, 2012). The physicians are members of the Statutory Health Insurance Physicians (Kassenärztliche Vereinigung, KV) of their region (BMG, 2013c). The KV has the task to discuss with regional associations of sickness funds about the reimbursement of contractual medical services (BMG, 2013c). This will be explained below.

Respondents G showed that the GPs in Germany are willing to listen to the demands of patients. If patients demand blood tests, then the GP will make sure that the patient gets these tests. In Germany the lab results are more important for the GP than the symptoms of the patient. It was also stated that blood and other diagnostic samples are taken at the GP office, instead of 'prikposten' in the Netherlands. The diagnostic samples (blood for example) are collected at the GP by a collection service of the private laboratories. The samples are then analyzed at the laboratories and the results are sent back to the GP. If blood is collected in the morning at the GP, then patients receive the results and their diagnosis at the same day.

Patients

In Germany, the reinforcement of the rights and competencies of patients is an important concern for the health care policies (BMG, 2013b). An example of this is that representatives of patient organizations take place in meetings of the Federal Joint Committee (Gemeinsamer Bundesausschus, G-BA)[20]. There is also a staff function in the G-BA, which is primarily concerned with the needs of the patient (BMG, 2013b). So at the institutional level, the patients do have some involvement in the regulatory processes. Diagnostic procedures, as well as therapeutical procedures, are to be agreed with the patient (BMG, 2013b). So at the individual level, it is the patient who determines its diagnostic or therapeutical procedure in the end.

The Industrial System

The second determinant of the German primary diagnostic system is the Industrial System. As for the Netherlands, the Industrial System in Germany is divided into the manufacturers of in-vitro diagnostic devices/supplies and the organizations involved in the collection and analysis of the in-vitro diagnostic process. This is because these types of organizations are the main actors in the diagnostic process since they manufacturer the in-vitro diagnostic devices and analyze the diagnostic samples.

Private Laboratories

In Germany the analysis of diagnostic samples can be executed at private diagnostic laboratories and at laboratories connected to hospitals (hospital laboratories) (Gässler, 2012). According to a professor of the center for laboratory diagnostics at the St. Bernward Hospital, there are about 200 laboratory practices in Germany, but half of them only operate regionally (Gässler, 2012). It is expected that in the near future a maximum of five nationwide networks of laboratories will be sufficient, with only a few locations (Gässler, 2012). Currently, there are already (inter)national groups of laboratories with regional departments (labs) in Germany. According to Knipp (2011), there were about seven large laboratory groups in 2011 in Germany. These groups are Sonic Healthcare, Synlab, Amedes, Staber, Kramer and Limbach (Knipp, 2011). The last of the large groups of medical diagnostic laboratories is Labco (Labco, 2014a). Labco is specialized in providing medical services throughout its local network in six countries in Europe, namely Belgium, France, Germany, Italy, Portugal and Spain (Labco, 2014a). Originally seven laboratories in Germany belonged to the local network of Labco (Labco, 2014b). But in 2013, Labco sold its German subsidiaries (the seven local laboratories) to the other large group Sonic Healthcare (Labco, 2014c).

In Germany, Sonic Healthcare is the largest laboratory medicine company (Sonic , 2014a). There are five large laboratories, next to the Labco group, in Germany belonging to the Sonic group (Sonic, 2014b). These laboratories differ in their focus. Labor Dr. Steinberg, for example, is primarily focused on cytopathology (Steinberg, 2014). The German laboratories belonging to the Sonic Healthcare network have close connections with diagnostic devices manufacturers such as Ariosa Diagnostics (Ariosa Diagnostics, 2013). Also the GLP Medical group in Hamburg belongs to the Sonic Healthcare network (Sonic, 2014b). The German laboratories belonging to the Sonic Healthcare network have close connections with diagnostic devices manufacturers such as Ariosa Diagnostics (Ariosa Diagnostics, 2013). Ariosa Diagnostics has developed a prenatal test for pregnant women. Another large group is Amedes (Knipp, 2011). In 2011, Amedes possessed about twenty laboratories all over Germany. The Limbach group possess about 25 laboratories in Germany. These groups of laboratories accounted, together with Staber, Kramer and Synlab, for about 70% of the in-vitro diagnostic market in 2011 (Knipp,

[20] The GBA will be explained below.

2011). Smaller groups of private laboratories are Labor Lademannbogen, The Schottdorf Group and Bioscientia (Lademannbogen, 2014; Schottdorf, 2014; Bioscientia, 2014b).

Hardly any private laboratory shows the amount of diagnostic tests that are conducted, but the MVZ Labor Saar, part of the Labco and Sonic group, shows that they conduct more than 5000 tests every day (Labor Saar, 2014). About 160 employees work at the MVZ Labor Saar.

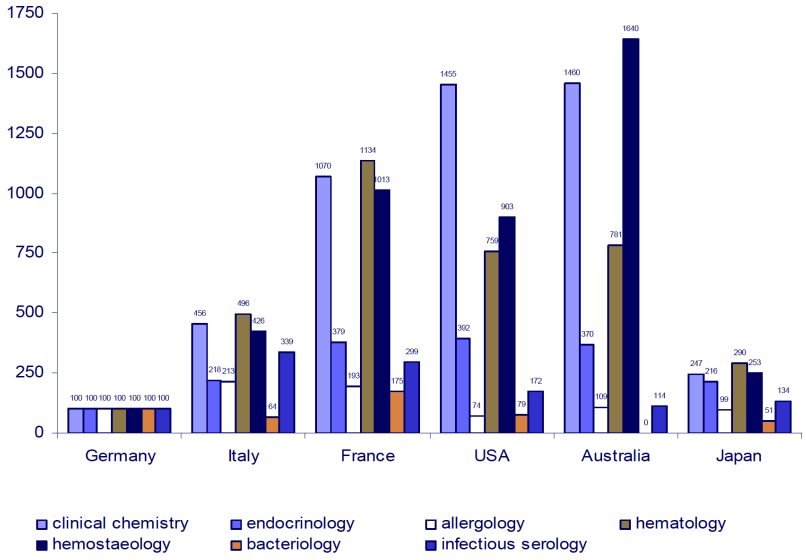

Figure 30. Efficiency of diagnostic testing per country (VDGH, 2011)

In figure 30 it is shown that the German private laboratories conduct their diagnostic tests far more efficient than other countries. Especially in the field of clinical chemistry, the German laboratories are far more efficient.

Hospital Laboratories

Diagnostic analysis can also be performed at hospitals. According to respondents G, several hospitals in Germany possess their own diagnostic laboratories. The Department of Clinical Chemistry/Central Laboratories of the University Medical Center Hamburg-Eppendorf (UKE), for example, does laboratory (medical) testing for all the departments of the UKE (UKE, 2013). At this department, approximately 3500 samples are analyzed every day, which leads to an average of 6.5 million results[21] a year (UKE, 2013). Another example is the Central Institute of Clinical Chemistry and Laboratory Medicine at the University Hospital Düsseldorf (UKD, 2014). At this institute about 3 million diagnostic laboratory test are performed each year (UKD, 2014). There were about 2200 hospitals in Germany in 2011, and about 150 of these hospitals had a laboratory physician at their disposal (Knipp, 2011). The market share of the hospital laboratories is loosing terrain to that of the private laboratories (VDGH, 2011). This is shown in figure 31. The market share, in terms of percentages of total health expenditures, is decreasing over time for the in-patient tests (hospital). The percentage of the out-patient tests (private laboratory) is increasing on the other hand. Respondents G explained that fierce competition between the private laboratories resulted in highly efficient laboratory processes. Therefore the private laboratories are able to analyze the samples to lower costs than the hospitals. The result

[21] One test could show multiple results

is that many hospitals mainly use their laboratories for emergency testing, and most tests are outsourced to the private laboratories.

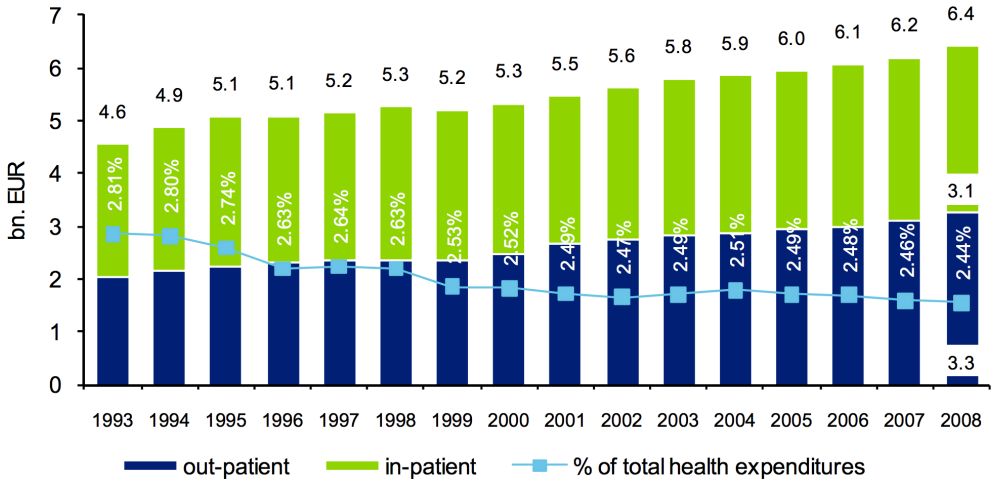

Figure 31, Market share of out-patient and in-patient testing in Germany (VDGH, 2011)

In Figure 32 the costs are shown for hospitals and university hospitals if the diagnostic activities are outsourced to a greater extend. The figure shows that if the diagnostic activities are outsourced to a greater extend, the costs of diagnostics also decrease to a greater extend (VDGH, 2011).

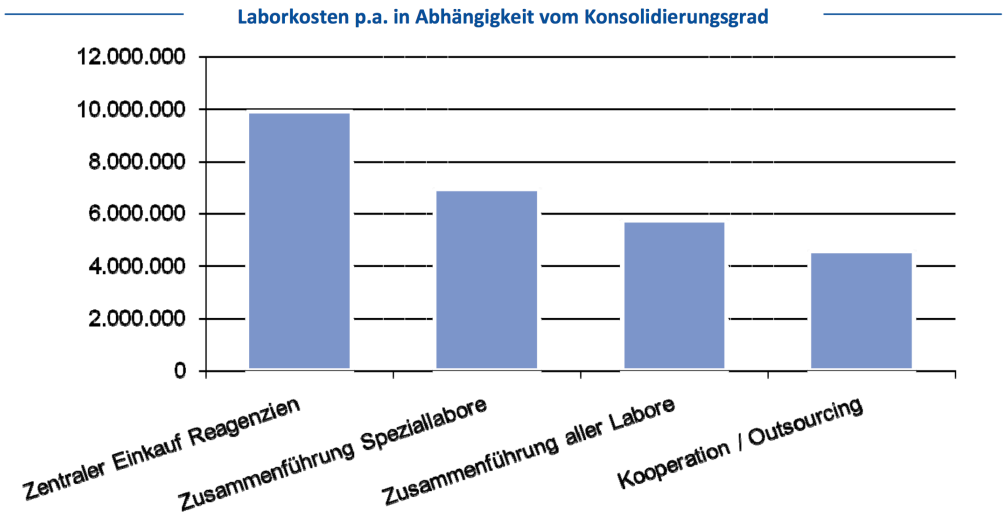

Figure 32. Cost of diagnostic testing for hospitals of out-patient and in-patient testing VDGH, 2011

Manufacturers

In Germany, the umbrella organization for manufacturers of in-vitro diagnostic devices is called the Verband der Diagnostica-Industrie (VDGH) (VDGH, 2014a). The VDGH has 99 member companies, which develop diagnostic and life science research devices (VDGH, 2014a). These 99 member companies account for approximately 90% of domestic sales in the diagnostic

market (VDGH, 2014a). About 60% of these companies conduct research in Germany and almost 70% have production facilities in Germany (VDGH, 2014a). Again by looking at the largest in-vitro diagnostics manufacturers as described by Renub Research (2010), the large manufacturers in Germany can be identified. The large manufacturers in Germany are Abbott Laboratories (Diagnostic Care), Beckman Coulter, Beckton Dickinson Company, BioMérieux, Ortho Clinical Diagnostics, Roche (Diagnostics), Sysmex, and Siemens (VDGH, 2014b). There are also smaller companies member of the VDGH, such as Numares Health, Concile GmBH (VDGH, 2014b). Also the VDGH is part of the European Diagnostic Manufacturers Association (EDMA) (EDMA, 2014a). The EDMA "is an international, non-profit organization representing the interests of the medical in vitro diagnostics industry in Europe" (EDMA, 2014b).

Respondents G showed that the relation between the manufacturers and laboratories is strong. This is because the laboratories become, on the one hand, dependent on their supplier (the manufacturer) of the in-vitro diagnostic devices. The laboratories often lease the devices and often more than one device is used from a single manufacturer. Therefore it is less interesting to switch between manufacturers, because then several devices, which are part of a whole operating system, need to be handed in to the original manufacturer again. On the other hand, the laboratories often use two or more manufacturers. So therefore they are able to substitute one for another if lower prices are offered. This gives them more buyer power to the other manufacturer(s). Both the manufacturers and laboratories therefore have supplier and buyer power, which has led to long time relationships.

The Political system

In figure 34, the German political system for the primary health care is shown. At the top is the Federal Ministry of Health (Bundesministerium für Gesundheit, BMG) (MIPH, 2013). The BMG is, primarily, the highest regulatory and supervisory authority in Germany (MIPH, 2013). The core task of the BMG is to safeguard and further develop the statutory health insurances (SHI). Other activities are health, prevention and long-term care (BMG, 2014). Relevant Federal authorities belonging to the BMG are the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel & Medizinprodukte, BfArM), the Federal Institute for Disease Control and Prevention (Robert-Koch-Institute, RKI) and the Federal Institute for Vaccines, Sera and Blood Products (Paul-Ehrlich-Institute, PEI) (BMG, 2014). The BfArM examines, inter alia, the safety of medical devices used for diagnosis (BfArM, 2014). The RKI is the central federal institution responsible for disease control and prevention (RKI, 2014). The activities of the PEI relate to the various duties laid down in German/European medicinal product legislation (PEI, 2014). The PEI is engaged in the fields of biological medicinal products, vaccines for humans and animals, medicinal products containing antibodies, allergens for therapy and diagnostics, blood and blood products and tissue for medicinal products for cell and gene therapy (PEI, 2014). The PEI also tests in-vitro diagnostic medical devices by a testing laboratory at the institute (PEI, 2014).

Next to the BMG, there are State Ministries of Health, which are primarily concerned with the provision of health care by managing disease registries, prevention and the management of infection outbreaks (BMG, 2014). Next to these ministries, there are the public health services (Öffentlicher Gesundheitsdienst, ÖGD). These are local public health services, which monitor local institutions such as hospitals and they provide various kinds of counseling services (BMG, 2014).

There are also relevant self-governing institutions[22] present in Germany (MIPH, 2013). The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) "is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany." (G-BA, 2014) The G-BA represents the interests of over 70 million people in Germany. The G-BA specifies which services in the medical care are reimbursement by the statutory health care funds, and specifies measures for quality assurance of medical care for the patients (G-BA, 2014). The members of the G-BA are delegates from the Doctors' National Association of Statutory Health Insurance (referring to physicians), the German Hospital Federation and representatives of patients and the government (MIPH, 2013). If propositions are approved by the G-BA, they are forwarded to the BMG, who can then endorse or reject the proposal (MIPH, 2013). Figure 33 shows the key role of the G-BA in the German institutional setting.
Also relevant is the Institute for Quality and Efficiency in Health Care ("Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen", IQWiG) (MIPH, 2013). The IQWIG is an independent research institute that aims to objectively examine the (dis)advantages of medical services (MIPH, 2013). The IQWIG writes independent, evidence-based reports on, for example, methods for diagnosis, and thereby provides information to the G-BA, BMG and the general public (MIPH, 2013).

In Germany, there is the Federal Health Insurance (Kassenärztliche Bundesvereinigung, KBV), which is the political advocacy for office-based physicians and psychotherapists at the national level in Germany (KBV, 2014a). The KBV is an institution for medical self-management in the statutory health insurance and is a public corporation (KBV, 2014a). The main tasks of the KBV are the political representation of the interests of independent physicians at the federal level (KBV, 2014b). Other tasks are, inter alia, the representation of physicians to the health insurance companies, and the participation in the federal joint committee (G-BA) (KBV, 2014b). The KBV consists out of seventeen regional physicians associations (Kassenärztlichen Vereinigungen, KVs), spread across Germany (KBV, 2014c). The task of the KV is to discuss and agree with the regional associations of sickness funds about the reimbursement of contractual medical services (BMG, 2013c). This is also discussed by respondents G. They stated that the KVs have the budget for the reimbursement of the different types of physicians. So also for the in-vitro diagnostic system, the KV has the budget and divides this by power and size of the specialists groups. The KV has a list with the compensation tariffs for the diagnostic procedures and analyzes.

[22] An institution not controlled by outside forces

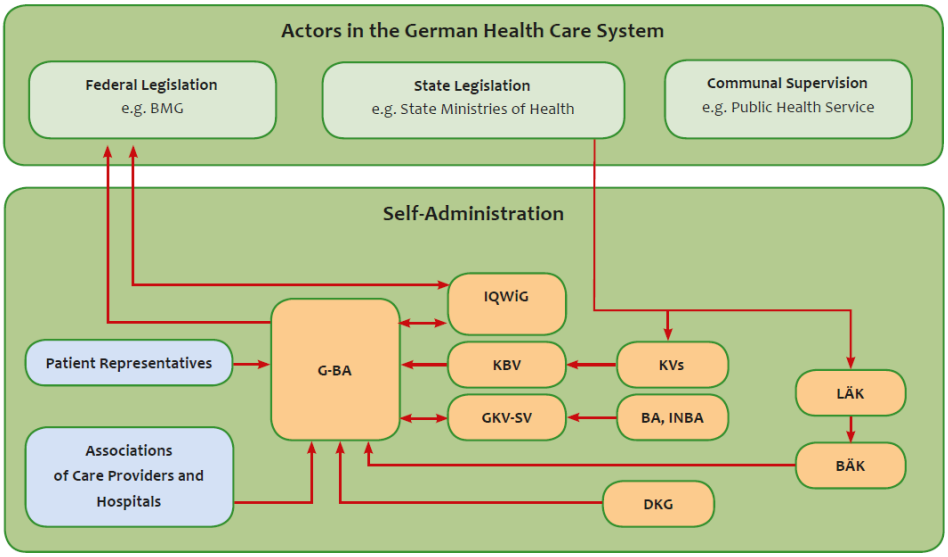

Figure 33 German Institutional setting (MIPH, 2013)

Intermediaries

Between the Educational system and the Industrial System are the Intermediaries. The Intermediaries are divided into Research Institutes and Brokers.

Research Institutes

In Germany, several relevant research institutes and companies can be identified. The companies described below belong to the Diagnostic Net BB network in Germany (Diagnostiknet, 2014b). Diagnostik Net BB facilitates its members, highly innovative companies and research institutes, with services along the entire value chain (Diagnostiknet, 2014a). The Fraunhofer Institute for Biomedical Engineering (IBMT) is an institute where scientists conduct research in the field of, inter alia, molecular diagnostics, lab-on-chip technologies, and nanobiotechnology (Diagnostiknet, 2014a). The Experimental and Clinical Research Center (ECRC) is the result of a partnership between university hospital Charité and the Max Delbrück Center for Molecular Medicine (MDC) (Diagnostiknet, 2014a). At the ECRC, the scientists develop new strategies for diagnosis, prevention and also the therapy for different kinds of indications (Diagnostiknet, 2014a). ThermoFisher Scientific "investigates, develops and produces novel diagnostic tests to optimize diagnostics and treatment of life-threatening diseases"(Diagnostiknet, 2014a).

Brokers

The German United Society for Clinical Chemistry and Laboratory Medicine (DGKL) has been founded in 2003, through the merger of two medical scientific societies named the German Society for Clinical Chemistry (DGKC) and the German Society for laboratory medicine (DGLM) (DGKL, 2014b). The main goal of the DGKL is to represent, promote and develop the clinical chemistry and laboratory medicine in the area of research, teaching and health care (DGKL, 2014a). The DGKL aims to promote research in all areas of laboratory medicine and clinical chemistry in order to improve the diagnosis and care for patients, to assist the physician and to achieve the further expansion of the clinical chemistry industry (DGKL, 2014a). Some of the tasks of the DGKL are to professionally qualify young scientists, and thereby to provide these scientists with medical training and further education (DGKL, 2014a). The DGKL also organizes scientific meetings for scientists and physicians in this field, and also implements projects in

research and teaching (DGKL, 2014a). The DGKL develops measures in order to improve the early detection, diagnosis, course assessment and monitoring of diseasing, as well as the medical care (DGKL, 2014a). The DGKL is also involved in the publication of certain scientific journals (DGKL, 2014a).

In Germany, there are also laboratory communities (laborgemeinschaft). These laboratory communities are defined, by the federal community of contract physicians (des Bundesmantelvertrages-Ärzte , BMV-Ä), as a community body of contract physicians which serves the purpose of providing medical laboratory analyzes in the same shared establishment (a laboratory) (Ministry of Finance, 2009). Laboratory communities exist in different organizational forms. These forms range from service companies, to accounting units and even to a laboratory community with a separate operating management (laboratory). Respondents G stated that the laboratory communities often do not posses their own laboratory, but are established to bundle all the requests of multiple physicians and let these tests be analyzed by a private laboratory.

The private health insurance association (Verband der Privatenkrankenversicherung, PKV) represents the general interests of the private health insurances, the private health insurance companies (member firms) and thereby the interests of the private long-term care (PKV, 2014). By taking part in parliamentary hearings, the association takes stand on regulatory issues. The association also gives advice to its members (private insurance companies) on fundamental issues such as new tariff introduction. The Central Federal Association of Health Insurance Funds (GKV-Spitzenverband, GKV-SV) is the central representative at the federal level of the statutory insurances of Germany (MIPH, 2013). The main task of the GKV-SV is their responsibility for the determination of payments for each medical treatment (of which also diagnostic services) and the costs for medical goods (MIPH, 2013; GKV-SV, 2013).

The Educational System

Education is also a determinant of the National Innovation System. Education has been divided into clinical chemistry/laboratory medicine and education for the GP.

Clinical chemistry/laboratory medicine

Education concerning clinical chemistry and medicine laboratory can be attended at universities. At the University Medical Center Hamburg-Eppendorf (UKE), the Clinical Chemistry Department is actively involved in educating their students in the field of clinical chemistry, and also continuing education for physicians concerning clinical chemistry (UKE, 2013). This is also the case for the University Hospital Leipzig (UKL), where both students and physicians can be educated and trained (UKL, 2014).

But also the diagnostic laboratories offer trainings and education. Bioscientia, for example, offers physicians of all specialties in established practices and hospitals regular training events (Bioscientia, 2014a). Bioscentia is part of the Sonic Healthcare group (Sonic, 2014). These trainings are all focused on activities in the laboratories and physician practices (Bioscientia, 2014a). The topics of these trainings are often chosen from aspects of both new developments in the medicine laboratory field, and their practical relevance according to the latest publications (Bioscientia, 2014a).

Also the German Society for Clinical Chemistry and Laboratory Medicine (DGKL) promotes the education and continuing education of physicians, as well as the continuing education of natural scientists (DGKL, 2014a). More specifically, the DGKL provides biochemists, biologists, chemists, and medical doctors with the opportunity to become a clinical chemist (DGKL, 2014b)

Physician/General practitioner
Since 2002, the education and licensing regulations have changed for physicians in Germany (BMG, 2013c). Contents were modernized, new forms of teaching were obtained and new test methods were introduced (BMG, 2013c). Medicinal training in Germany only takes place at universities (Daad, 2011). There are 35 state universities and one private university where students can enroll in the medicine program (Daad, 2011). A university degree in medicine takes about six years, and the minimal trainings period for GPs is 5 years (BMG, 2013c; EUprimarycare, 2014).

Infrastructure
Standard and norms
Close to the political system, there are the standard and norms in the in-vitro diagnostic system. In Germany, there is the Act on Medical Devices. The purpose of this act is "to regulate the trade in medical devices and, by doing so, to guarantee the safety, suitability and performance levels of medical devices as well safeguard the health and ensure the necessary protection of patients, users and other persons"(BMG, 2011, p.1). These medical devices could refer to in-vitro diagnostic medical devices (BMG, 2011). If this is the case, then the medical devices will have to comply with the 'Directive 98/79/EC on In-vitro Diagnostic Medical Devices (IVDMDD)' regulation, according to a presentation of the Federal Ministry of Health of Germany (BMG, 2009). The philosophy behind this is that general requirements such as safety and performance, as well as that harmonized standards will provide insights in the technical details (BMG, 2009). The CE-mark allows the products to be traded without restrictions on the Community market (BMG, 2009). The CE-mark has been explained in the Dutch National Innovation system above. The manufacturer, or his/her representative, is the person who is responsible for the first placing on the market of the device (BMG, 2011). The diagnostic products have to comply with the European Medical Device Directives (Medical Device Directive 93/42/EEC, Active Implantable Medical Devices 90/385/EEC and In Vitro Diagnostic Medical Device Directive 98/79/EC) (European Commission, 2014). The Federal Ministry of Health does have a supervisory function, but a competent authority will be selected in order to carry out the tasks concerning the assessment of procedures (BMG, 2011). The competent authority has to monitor compliance with the obligations and requirements for the medical devices (BMG, 2011). The Medical Device Safety Service (MDSS) is such an organization (MDSS, 2014). MDSS is specialized in national registration of devices, clinical evaluation, CE mark services and more (MDSS, 2014). The Federal Ministry of Health reports this to the Federal Ministry of Economic Affairs, who will then, on its turn, inform the Commission of the European Communities (BMG, 2011).

Next to the Act on Medical Devices, there is the Act on Medicinal Products (BMJ, 2013). "It is the purpose of the present Act to guarantee, in the interest of furnishing both human beings and animals with a proper supply of medicinal products, safety in respect of the trade in medicinal products, ensuring in particular the quality, efficacy and safety of medicinal products in accordance with the following provisions." (BMJ, 2013). Medicinal products could refer to substances or preparations made from substances that are used in order to make a medical diagnosis (BMJ, 2013).

The diagnostic laboratories have to comply with the Directive of the German Medical Association for quality assurance of medical laboratory investigations (RiLiBÄK) (BundesArztekammer, 2014).

Health insurance

The German Federal Insurance Authority (Bundesversicherungsamt, BVA) is an independent superior federal authority in Germany (BVA, 2014). With regard to the legal supervision of the statutory health and long-term care insurance, the BVA collaborates with the Federal Ministry of Health (BMG) (BVA, 2014). Tasks of the BVA are, for example, the approval of insurance provider regulations, the management of subsidies and other allocations made to the social security system and the supervision of federally regulated social security insurance providers (MIPH, 2013). The Federal Financial Supervisory Authority (Bundesanstalt für Finanzdienstleistungsaufsicht, BaFin) is an independent public regulatory institution, and its main task is to ensure the proper functioning, stability and integrity of the German financial system (MIPH, 2013; BaFin, 2014). The BaFin is relevant for private insurances (MIPH, 2013).

The Health insurance system is divided into the statutory health insurance funds and the private health insurance funds. Anyone working in Germany is usually compulsorily insured, which means that they are automatically covered by statutory health insurance (Deutsche Sozialversicherung, 2014a). The people who are compulsory insured, are in principle all workers with a gross pay that does not exceed a defined upper limit (in 2014 this was €4,462/month) (Deutsche Sozialversicherung, 2014b; Euroaxess, 2014). In figure 34 the health insurance system is shown.

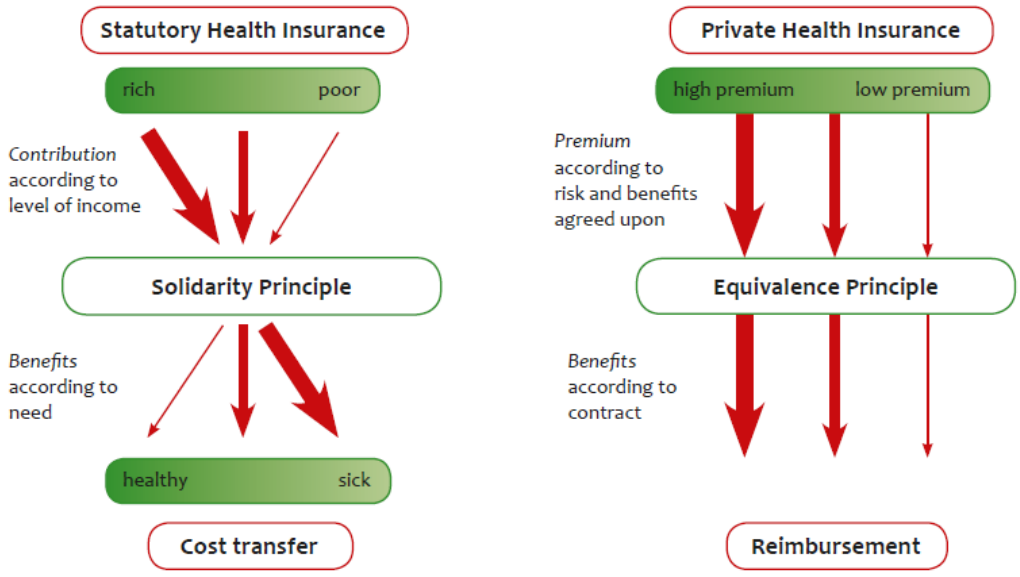

Figure 34. The German health insurance system (Deutsche Sozialversicherung, 2014a)

Citizens who are voluntarily insured are still entitled to a supplement towards the contributions of their employer (Deutsche Sozialversicherung, 2014c). The basic funding structure is based on the solidarity principle, as explained above. The largest private health insurers are Debeka, DKV, Axa, Allianz and Signal Iduna (MIPH, 2013).

Statutory health insurance is not provided by one central fund, but by several health insurance funds (Deutsche Sozialversicherung, 2014d). Those funds are self-administering corporations under public law, and they are organized into associations (Deutsche Sozialversicherung, 2014d). Self-administration refers to the involvements of insured persons and employers in

shaping the policies followed by the health insurance funds (Deutsche Sozialversicherung, 2014d).

Framework conditions

Financial Environment

The fee system for the GPs consist of a flat-rate annual fee, independent from the number of contacts, a flat-rate fee for extended treatments and a flat-rate fee for the treatment of chronically ill patients (UEMO, 2010). The purpose of this fee system, which is not based on the amount of contacts, is to reduce the frequency of patient-physician contacts in Germany, which was the highest in the world in 2010 (17.9 contacts per capita per year) (UEMO, 2010). On the other hand, this fee system should increase the amount of time available for consultation with each patient (UEMO, 2010).

Statutory health insurance in Germany is financed through both the contribution of employers and the insured people (employees) (Deutsche Sozialversicherung, 2014c). "The contribution amount depends both on an employee's assessable income up to a defined contribution assessment limit, which is adjusted each year and on the contribution rate" (Deutsche Sozialversicherung, 2014c).

In this statutory health insurance system, there is a legally stipulated contribution rate of 15.5 percent in order to be insured (Deutsche Sozialversicherung, 2014c). The 15.5 percent is divided amongst the employer (7.3%) and the employee (8.3%) (Deutsche Sozialversicherung, 2014c). According to respondents G, the laboratory sends their bill to the KV and the KV reimburses the laboratory. The KV then collects the money from the health insurance companies. In the private insured reimbursement system, the patients directly pay the laboratory and thereafter collect their reimbursement from the health insurance companies. The Gebührenordnung für Ärzte (GOÄ) regulates the accounting of all medical services that are not covered by the statutory insurance system (Fairfekt, 2014).